

MANAGEMENT *of* PAIN
in CANCER

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in CANCER

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Preface

THE AIM of this book is to guide the family physician in his efforts to mitigate the agonies of terminal malignancy. We have accordingly marshaled descriptions of all the pain relieving procedures that we have found useful in our own experience. The most common approach—the use of analgetic drugs—is presented first in the hope of providing some helpful methods of using the familiar agents as well as the newer synthetic analgetics and opiate antagonists. The subsequent chapters present descriptions of clinical procedures to help the general practitioner achieve technical competence in their performance or have a better understanding of the contributions that can be made by experts in specialized fields of medicine and surgery. We have sought to give expression to differences of opinion regarding the use of these procedures in order to provide a clear appreciation of the problems relating to the management of terminal malignancy. In recognition of the fact that it is not the patient alone who suffers, we have also concerned ourselves to some extent with the reactions of the family and the attending physician.

We have tried to provide information regarding means of alleviating the misery and sorrow as well as the pain that closes the cancer episode

We are indebted to Dr Harry Beckman for suggesting the preparation of this book and for his most valuable criticism and encouragement We owe heartfelt thanks also to our colleagues for their generous assistance and advice The publisher contributed more than skilled technical assistance the confidence and co-operation of his staff during the preparation of the book lightened our task immeasurably

Foreword

THIS VOLUME deals with a subject neglected far too much by the medical profession and accordingly serves an important function by contributing to the scant knowledge in this field. The large number of persons developing cancer and the many who have severe pain in the terminal stage of the uncured disease make the subject of vital importance.

In the seven chapters constituting this volume the authors discuss numerous phases of the treatment of pain including analgetics, nerve blocks, neurosurgical aspects, chemotherapy, surgical procedures, radiation and psychogenic aspects. The inclusion of these several mechanisms indicates that no single one will be efficacious in all patients and emphasizes the necessity of utilizing all possible methods in controlling pain.

Unfortunately, practically all the drugs that are really effective in controlling pain are habit producing and therefore must be used sparingly. Nerve blocks which are very important in therapy because they are reasonably effective and can be done without an operation, require great skill in injecting the anes-

thetic agent into the right areas and in proper amounts. Regardless of the type of therapy used there is a tendency to blame a poor result on the "neurotic condition" of the patient and this situation allows the patient to slide rapidly into drug addiction. We must appreciate that severe constant pain of the type commonly present in terminal cancer will destroy the morale of the sturdiest individual. Moreover the devastating effect of severe pain will make the patient particularly susceptible to the various discomforts present in terminal cancer and thus lower his pain threshold. The physician must recognize these conflicting factors and accept them as part of his responsibility rather than neglect the patient because he may be developing a neurotic tendency.

On many occasions the terminal phase progresses so rapidly that there is not enough time between onset of the severe pain and death for addiction to a narcotic to become very important and under such conditions analgetic treatment fills the need quite satisfactorily. But since it is extremely difficult—in fact impossible—to predict duration of life with cancer we are often loathe to give liberal amounts of narcotics because the drug addiction itself may become a hideous spectacle and actually result in great misery for the patient.

In their discussion of therapeutic measures the authors have appropriately included operative procedures of a palliative nature. This is an important aspect of therapy in a patient with terminal cancer because relief from one discomfort or pain may make the remaining one or others bearable. As is emphasized in

Chapter V, the indications for these palliative procedures are by no means clear. For example it is well known that resection of a carcinoma of the rectum or colon is desirable even though there may be metastases in the liver. That removal of the ulcerating tumor mass eliminates the loss of blood and serum from the ulcer and likewise minimizes terminal pain which is usually very severe in patients who do not have the rectal lesion excised. However good judgment is necessary in choosing the patients, since an unsuccessful attempt to remove the involved bowel might make the tumor grow much more rapidly—if for instance tumor tissue was cut across during the operation.

For reasons presented here and in the text, we must take advantage of all possible measures to reduce the discomfort and pain of terminal cancer. The authors are to be congratulated for having covered these various points in an admirable fashion and for having devoted the proper attention to the details of the various types of therapy.

—WARREN H. COLE.

Table of Contents

I	SYSTEMIC ANALGETICS <i>by</i> M J SCHIFFRIN and E C GROSS	13
	General Considerations	13
	Nonaddicting Drugs	15
	Addicting Drugs	16
	Adjuncts and Miscellaneous Agents	31
II	NERVE BLOCKS FOR PAIN IN MALIGNANCY <i>by</i> MAX S SADOVE and REUBEN C BALAGOT	34
	Principles of Nerve Blocking	34
	Different Types of Blocks and Techniques	39
	Agents Used for Blocks	49
	Blocks for Different Regions	52
	Premedication	84
	Reactions to Local Anesthetics	84
III	NEUROSURGICAL ASPECTS OF PAIN MANAGE MENT <i>by</i> OSCAR SUGAR	86
	Peripheral Nerve Section	86
	Cranial Nerve Section	87
	Nerve Root Section	89

	<i>Table of Contents</i>	11
	Spinothalamic Chordotomy	94
	Spinothalamic Tractotomy	97
	Stereotaxic Lesions	100
	Frontal Leukotomy	101
	Miscellaneous Procedures for Relief of Pain	105
	Neurosurgical Aspects of Pain by Region	108
IV	HUMORAL AND CHEMICAL PALLIATION OF MALIGNANCY <i>by</i> SAMUEL G TAYLOR III <i>and</i> M J SCHIFFRIN	111
	Clinical Management of Malignancy	114
	Pharmacologic Properties of Hormones and Drugs	133
V	SURGICAL PROCEDURES IN CONTROL OF PAIN IN ADVANCED CANCER <i>by</i> HENRY SCHWARZ II	146
	General Considerations	147
	Specific Situations Requiring Surgical Intervention	152
VI	RADIATION THERAPY IN THE RELIEF OF PAIN IN MALIGNANT DISEASE <i>by</i> J W J CARPENDER	181
	Radiation Combined with Chemotherapy and Surgery	183
	Prevention of Pain	184
	Quality of Radiation	184
	Artificial Radioactivity	185
	Metastatic Disease and Local Extension	188
	Other Complications	190
	Radiation Sickness	191

VII · PSYCHOLOGICAL ASPECTS OF PAIN IN TERMINAL MALIGNANCIES <i>by</i> v RICHARD ZARLING	193
General Considerations of Pain	194
Mental or Psychological Factors in Pain	200
Modification of the Pain Reaction Pattern by Psychological Support	216
Modification of the Pain Reaction Pattern by Hypnosis	221
Index	227

CHAPTER 1

Systemic Analgetics

GENERAL CONSIDERATIONS

THE USE OF any systemic analgetic should be considered in relation to a number of factors such as the degree of pain the clinical condition of the patient the immediate prognosis the proposed therapy and the probability of its success life expectancy and the ability of the patient to carry on a normal role in society The prognosis in malignancy is not necessarily related to the degree of pain For example prostatic carcinoma with extensive metastases may have a negative prognosis yet the pain from the metastatic involvement may be so slight as to be controlled by aspirin The choice of analgetic therefore should rest primarily on the degree of pain Most pain situations are acute and analgetics are consequently used as a temporary device pending direct attack on the cause of pain In the presence of malignancy however the effectiveness of surgery chemotherapy and radiation is often in doubt and the physician must be prepared to provide for relief of chronic rather than acute pain The life expectancy will influence the choice of

agents used For example if the prognosis indicates a terminal course that can be measured in weeks every effort should be made to provide relief of pain regardless of such considerations as addiction The medical and social problems of addiction are unimportant when the few remaining days of life need the blessed relief provided by the opiates This is important not only to the patient but to the members of his family who suffer with him Addiction and particularly tolerance are important in the patient with long term chronic pain In such instances every effort should be made to put off the use of the potent addicting drugs until all other measures have been exhausted The patient may have a year or more of life important to himself, his family and society The analgetics used in such circumstances should provide adequate pain relief with a minimum of interference with his normal functions and behavior Whenever possible in such conditions nonaddicting drugs should be used If these prove inadequate, codeine is the drug of choice because of its relatively low addiction potential If opiates or opioids must be used, oral medication is preferred It is important to inform the family of the characteristic effects of the opiates (such as tolerance addiction and nausea) so that they can make a satisfactory adjustment to the patient's subsequent behavior and symptoms

The fear of intolerable pain is best overcome by conditioning the patient to expect relief after administration of the analgetic This can be achieved by in

sure the adequacy of the dose and by giving the drug promptly on the appearance of pain. Pain itself is a most potent antagonist not only to the untoward effects of the analgetics but to the analgesia itself. Therefore full doses should be given when the pain is moderate instead of waiting until the patient writhes in pain. The fear of pain and the individual reaction to pain can also be modified by the use of agents other than the analgetics such as barbiturates, amphetamine and other drugs that affect the emotional plane and sensorium.

NONADDICTING DRUGS

The salicylates, paraminophenols and pyrazolones (as exemplified by aspirin, phenacetin and antipyrine respectively) are nonaddicting drugs with moderate analgetic effect. They are of little or no value in deep visceral pain. Combinations of this group of agents with barbiturates, sympathomimetics, caffeine or codeine are useful and often may be employed to greater advantage than the individual components used singly. The continued use of these agents for chronic pain carries the risk of increased possibility of toxic reactions.

Cinchonism or salicylism following the use of salicylates resembles quinine intoxication. Visual and auditory disturbances, tachycardia, hyperpnea, central excitation and lowered prothrombin values are among the signs of salicylate intoxication. Severe salicylate toxicity can produce dyspnea, central nervous system

depression renal dysfunction and respiratory failure. Although the paraminophenols (for example phenacetin) are not addicting agents they are habit forming. The signs of chronic toxicity are sometimes easily confused with symptoms arising from the patient's primary disease. Among these indications of paraminophenol toxicity are cyanosis, a typical bluish color of the mucous membranes, anorexia, secondary anemia, leukocytosis, jaundice and oliguria. The pyrazolones (antipyrine for instance) may produce toxicity resembling that of the paraminophenols with the exceptions that cyanosis and methemoglobinemia are not characteristic. Antipyrine toxicity is commonly indicated by pink to purple macular patches, whereas the use of aminopyrine is accompanied by the danger of agranulocytosis.

ADDICTING DRUGS

At least two considerations must be understood and appreciated in order to provide for the intelligent choice and use of the addicting analgetics. They are tolerance and analgetic intensity.

Tolerance for practical purposes in the management of pain in malignancy can be defined as that characteristic which requires increasingly larger doses to provide the same effect as was produced by the original dose. For example 10 mg ($\frac{1}{8}$ gr) morphine may be an adequate dose in a hypothetical case but as the drug is used regularly over a period of time it no longer proves effective and 30 mg ($\frac{3}{8}$ gr) may be

needed to give the same pain relief that was originally produced by one third that amount of morphine. Tolerance to addicting drugs begins early, in fact there is good evidence that it is operative after the very first dose. Factors facilitating the development of tolerance include the administration of the drug at frequent regular intervals and the use of successively larger doses. The appearance of clinically significant tolerance can be delayed by using the minimal effective dose as infrequently as possible and by limiting the use of addicting drugs to their primary characteristic analgesia and not to secondary properties such as sedation. The writing of such an order as "½ gr morphine q 4 h" is to be deplored. Addicting analgetics are to be ordered on the basis of pain, not according to the clock or nursing habits. Unfortunately cross tolerance exists among the potent analgetics. This means that if tolerance has developed to morphine it will also operate with similar drugs. For example using the hypothetical case referred to above, when 10 mg morphine was first used it was probably interchangeable with about 2 mg levorphan. After the development of tolerance at which time the morphine requirement was increased threefold more than 2 mg of levorphan would be needed if it were desirable to change to this drug. Thus one cannot change opiates without making allowance for the effects of tolerance. The need for increasingly larger doses may proceed to the point where pain relief becomes an economic burden.

The maximum analgetic intensity is a property pe-

cular to each of the potent analgetics. For every such drug there is a correlation between the dose and the intensity of analgesia *within certain limits*. It is the limit of this relationship with which we are concerned. For example, the maximum analgetic intensity (maximum increase in pain threshold) of codeine is achieved with about 65 mg (1 gr). Therefore, in a given case of acute pain, if this dose of codeine does not provide relief, little advantage is obtained from larger doses. The characteristic maximum analgetic intensity can be expressed in another fashion: every potent analgetic has a dose beyond which increments in dosage produce increasingly smaller increments in the intensity of analgesia. Examples of these critical doses are meperidine 150 mg and morphine 30 mg ($\frac{1}{2}$ gr).

The degree of maximum intensity of analgesia is usually measured as the maximum per cent increase in pain threshold. Some maximums are: codeine, 50 per cent; meperidine, 60 per cent; and very large doses of morphine, approximating 100 per cent. Dihydro-morphinone and levorphan are examples of drugs which readily provide increases of 100 per cent. The clinical significance of these figures is that pain which does not respond to codeine is unlikely to be affected materially by meperidine. On the other hand, where large doses of morphine prove unsatisfactory, good analgesia may be obtained with such drugs as dihydromorphinone or levorphan.

The toxicity of the addicting analgetics is sufficiently well known to require no elaborate exposition here. Attention might, however, be invited to a few basic

considerations sometimes overlooked. The morphine-like drugs are depressant except in their action on the vomiting center, the lower sections of the spinal cord and the gastrointestinal tract where they are primarily excitatory. The effects on the gastrointestinal tract include delayed gastric emptying time and constipation. It is surprising how often the former is forgotten and patients are given oral medication shortly after administration of an opiate. Since there is considerable variation in the individual response to any opiate, it is often advantageous to rotate the drugs being used in order to achieve maximum effectiveness with a minimum of untoward reactions.

The cause of death from opiate intoxication is respiratory failure. Severe opiate-induced respiratory depression is treated specifically by the intravenous administration of nalorphine (Nalline 5 mg) or levallorphan (1 mg). These drugs should be given until the desired respiratory response is obtained. Overdosage should be avoided since these narcotic antagonists have depressant effects and, when given to excess, will themselves produce respiratory depression. Patients requiring treatment with such agents should be observed closely for at least 24 hours. The antagonists will reverse or inhibit all the pharmacologic effects of the opiates, including respiratory depression and analgesia. When given to an addict, the narcotic antagonists will provoke violent abstinence symptoms.

An interesting use of the antagonists is to combine them with an opiate in order to permit administration of a larger dose of the analgetic without increased risk.

of respiratory depression Cullen and Santos (A M A Arch of Surg 69 410 1954) used a combination of 5 mg levorphan and 0.5 mg levallorphan to obtain an analgesia without respiratory depression in patients with chronic pain Not all of the narcotic analgetics have been studied as yet regarding the specific ratio of opiate to antagonist

Included among the opiates are such drugs as codeine dihydrocodeinone morphine 6-methyl-dihydro-morphinone and dihydromorphinone The opioids are synthetic addicting analgetics such as meperidine methadone alphaprodine and levorphan All agents in this group are subject to the Harrison Narcotic Act Their general characteristics dosage forms and routes of administration are listed below The suggested doses are those which will produce approximately the same rise in pain threshold as 10 mg ($\frac{1}{4}$ gr) morphine sulfate

CODEINE

Codeine is available as the free base or in the form of water soluble phosphate or sulfate salts Pharmacologically it resembles morphine except as listed below Codeine is an addicting drug but its addiction potential is less than that of any of the other opiates It will produce a maximum increase in pain threshold approximately half as great as that of morphine These two factors serve to make codeine the drug of choice for moderate visceral pain If a nonaddicting agent is incapable of providing satisfactory analgesia and an opiate must be used codeine should be tried before

the more potent and more addiction liable drugs. Codeine although it will produce constipation generally provokes fewer unfavorable reactions than equivalent doses of morphine. It has a shorter duration of action and produces less euphoria, sedation and respiratory depression than morphine. Toxic doses of codeine lead to excitation rather than depression. The analgesia of codeine also differs from that of morphine in that codeine does not produce indifference to pain. Morphine and the other potent drugs affect the patient's reaction to pain in such a fashion that, although the patient recognizes the pain he often says "It feels as though it's happening to someone else."

Although combinations of codeine with salicylates, caffeine, etc. are often used to advantage, the maximum effect of codeine is not attained when the drug is given orally. When pain results from a condition such as malignancy it is advisable to give codeine subcutaneously in order to achieve the maximum analgetic effect. Because codeine is not commonly used by opiate addicts the erroneous impression persists that it is not an addicting drug. Its continued use however will produce tolerance and the entire sequence of addiction. Thus, physical dependence, gastrointestinal disturbances, emaciation, etc. are consequences of the continued use of codeine. The most effective dose is 65 mg (1 gr) either subcutaneously or intravenously. There is no advantage in the use of larger doses save in the presence of tolerance. The maximum analgetic effect is reached 30-60 minutes after subcutaneous injection.

DIHYDROCODEINONE

Dihydrocodeinone (Hycodan, Diconid) has the same chemical relationship to dihydromorphinone (Dilaudid) as codeine has to morphine. It is more potent than codeine on a weight basis and has a greater addiction potential but otherwise differs little from codeine. The usual oral dose of the bitartrate salt is 10 mg.

MORPHINE

Morphine is the classic opiate for the relief of severe pain and is the standard against which all the other potent analgetics are measured. Given orally, it produces little analgesia and therefore the parenteral routes are preferred. In the presence of acute overwhelming pain morphine may be given intravenously since this method provides the quickest and most intense analgesia. When morphine is given subcutaneously the maximum analgetic effect is obtained in 60-90 minutes. This analgesia is not so intense as that provided by intravenous administration but it is more prolonged. There are diminishing returns when doses larger than 10 mg ($\frac{1}{4}$ gr) are used in the absence of tolerance. Indeed, if this dose of morphine does not give adequate control of pain it may be advantageous to change at once to those drugs which will easily provide a 100 per cent increase in the pain threshold. Although larger doses of morphine are often used the resulting analgesia is accompanied by an increase

in the number and severity of undesirable reactions. Among the most common of such reactions are nausea, emesis, vertigo, miosis, hypnosis, respiratory depression, constipation, pruritus, oliguria and urticaria.

Morphine often produces a sense of well being beyond what might be expected to occur on the basis of the reaction to the relief of pain. This sense of well being is a desirable effect because the patient is comfortable and co-operative. If pain is still perceived the patient is indifferent to it. This alteration in the reaction to pain is one of the most valuable characteristics of morphine and the other potent analgetics. The patient is aware of pain but he feels that it is no longer part of him. He recognizes it as he would an impersonal object in the room and since his thoughts are no longer completely centered on pain he can think and act in a rational manner. The picture is completely different when euphoria results from the administration of a drug such as morphine; then the patient is definitely unco-operative and his thoughts are turned inward as he experiences a sense of exhilaration and exaltation. There are great differences in the individual responses to morphine; some patients experience a sense of well being, others euphoria. The reactions of any one patient to morphine are not necessarily the same as those which would be obtained if another opiate were used. The patient's response to euphoria will, to a great extent, be a reflection of his basic psychologic characteristics. To some individuals

this change in emotional plane will be more significant than any alteration of pain and the patient's demands for morphine will warn of the impending danger of addiction. It therefore becomes increasingly important to make certain that morphine be given for its primary indication—pain—rather than for a change in mood or emotional status.

Since the liver plays an important role in the detoxification of morphine, the drug will often produce exaggerated effects when given to a patient with hepatic disease. Morphine increases the cerebrospinal fluid pressure and this prevents its use when intracranial pressure is already increased. Among other conditions which contraindicate the use of morphine are pruritus, myxedema, acute renal damage and bronchial asthma.

DIHYDROMORPHINONE

Dihydromorphinone (Dilaudid, Hymorphan) is the most potent of the opiates on a weight basis. Since it is more effective orally than is morphine, 2–3 mg is given by this route. The subcutaneous dose is usually 2 mg. Although dihydromorphinone will produce a 100 per cent increase in the pain threshold, it has a shorter duration of action than morphine. Rectal suppositories containing 25 mg of the hydrochloride salt are used in an attempt to delay absorption of the drug and thus provide a longer duration of the analgetic effect. Dihydromorphinone is an addicting drug and the frequency with which it must be given for

chronic pain constitutes a serious disadvantage. The other pharmacologic effects of dihydromorphinone are similar to those of morphine with the following exceptions: reactions such as nausea, emesis and constipation are less severe and frequent, and sedation is not so marked as with morphine, an advantage when a hypnotic effect is undesirable. The euphorogenic properties of dihydromorphinone are less than those of morphine.

6 METHYLDIHYDROMORPHINONE

6-Methyldihydromorphinone (Metopon) is the methyl derivative of dihydromorphinone and has some of the parent compound's characteristics. It is more effective than morphine when given orally. The only dosage form commercially available is a 3 mg capsule. Reactions such as nausea, emesis and constipation occur less frequently than with morphine, and the hypnotic and euphorogenic effects are also less. This drug has an advantage over dihydromorphinone in that the duration of the analgetic effect is approximately the same as that of morphine. Although 6-methyldihydromorphinone is an addicting drug, it appears that tolerance develops relatively slowly and that there is a comparatively rapid dissipation of the abstinence syndrome when the drug is withdrawn. These considerations, however, do not alter the necessity for taking the same precautions that apply to any addicting agent. According to N N R (1955) the drug is recommended only for severe persistent pain.

MEPERIDINE

Meperidine (Demerol Pethidine isonipicaine) was the first successful synthetic substitute for morphine. Its pharmacologic properties which are related to morphine, codeine and atropine make meperidine a useful drug for the relief of moderate visceral pain. The usual dose is 50-100 mg orally or by intramuscular injection. The increase in pain threshold following the intramuscular administration of 100 mg meperidine is approximately the same as that of 10 mg ($\frac{1}{8}$ gr) morphine. In the absence of tolerance there is little to be gained from doses greater than 150 mg. One of the most important factors limiting the use of this drug is that it cannot provide much more than a 60 per cent increase in pain threshold. This means that if full doses (65 mg 1 gr) of codeine have been given without obtaining adequate control of pain in all probability meperidine will also fail.

The undesirable reactions to meperidine are vertigo, nausea, emesis, mydriasis and tachycardia. The frequency of vertigo limits the use of this drug in ambulatory patients. Neither a sense of well being nor euphoria is a characteristic consequence of the use of meperidine. Unlike most other opiates and opioids described in this chapter, meperidine intoxication produces excitation rather than depression. Meperidine has a wide margin of safety, but large toxic doses may provoke twitching, muscular incoordination, disorientation and convulsions. If the dose is very excessive

the period of excitement is followed by respiratory depression coma and death

The contraindications to the use of meperidine include increased intracranial pressure and severe hepatic disease Since meperidine is an addicting drug the usual precautions for such agents apply to its use

METHADONE

Methadone (Adanon Dolophine Methadon) was synthesized in Germany about the time of World War II Its advantages over morphine include oral effectiveness and the ability to provide a 100 per cent increase in pain threshold The usual dose is 10 mg, orally, but sometimes subcutaneously or intramuscularly According to N N R (1955) the intravenous route should not be used Since methadone produces local irritating effects the oral route is preferred but if parenteral administration must be used the size of the dose should be held to a minimum The oral effectiveness of methadone its analgetic potency and the lack of marked sedative effects help to make it a desirable drug in the management of chronic pain

Vertigo nausea and emesis are the most common undesirable effects attending the use of methadone Euphoria rarely occurs The depressive toxic effects of large doses are similar to those of morphine Although methadone is an addicting agent the abstinence syndrome following its withdrawal is much less severe although more prolonged than that of morphine This moderation of the abstinence syndrome

does not warrant indiscriminate use of the drug it should be used with the same caution as any other addicting agent

ALPHAPRODINE

Alphaprodine (Nisentil prisolidene Nu 1196) was synthesized by Ziering and Lee in 1947. Although less potent than morphine on a weight basis, alphaprodine has significant advantages over morphine. It is equally effective orally or by any parenteral route and it readily gives rise to a 100 per cent increase in pain threshold. The onset of the analgetic effect is very rapid and usually occurs within five minutes after subcutaneous administration. It is therefore not necessary to use intravenous or intramuscular injection for a rapid effect. The duration of effective analgesia is about one hour following a subcutaneous dose of 20 mg. This dose will produce approximately the same rise in pain threshold as will 10 mg ($\frac{1}{2}$ gr) morphine. Larger doses of alphaprodine will increase the intensity and duration of analgesia. Doses of 40–60 mg are frequently used in obstetrics. Just as the analgetic effects of meperidine resemble those of codeine, so the analgesia produced by alphaprodine is in many ways similar to that of dihydromorphinone. Although alphaprodine has been used most extensively for acute pain in obstetrics, urology and orthopedics, suitable doses provide the duration and intensity of analgesia needed for the control of any chronic pain. The flexibility of the drug over a relatively wide dosage range makes it adaptable to most pain problems.

The undesirable reactions to alphaprodine are, in general, the same as those to morphine except that respiratory depression is not as marked following the use of alphaprodine. It is an addicting drug and therefore the dose should be large enough to reduce the frequency of its administration for chronic pain.

LEVORPHAN

Levorphan (Levo Dromoran) is the levo optical isomer of 3 hydroxy N methylmorphinan tartrate. It is the most potent of the opioids on a weight basis. The subcutaneous injection of 2 mg produces an analgetic effect equal to that of 10 mg ($\frac{1}{2}$ gr) morphine and readily gives rise to a 100 per cent increase in the pain threshold. It is equally effective by any route of administration. Levorphan differs from morphine in that it has a longer duration of effect and constipation occurs infrequently. Experimental data in animals indicate that although the depth of respiratory depression is the same with both levorphan and morphine the duration of the depression is less with levorphan. The other pharmacologic effects of levorphan are much the same as those of morphine. The properties and characteristics of levorphan make it a useful drug for the most severe chronic pain.

Levorphan is an addicting agent and has no advantage over the other drugs in this respect. The contraindications and precautions attending its use are the same as those for morphine.

ABSTINENCE SYNDROME

The abstinence (withdrawal) syndrome appears when an opiate or opioid is abruptly discontinued after the development of addiction. The syndrome consists of an unmasking of excitatory phenomena. These have been described and measured by Hummelsbach. The symptoms vary in intensity and clinical significance. Among the milder and more moderate symptoms are yawning, lacrimation, perspiration, tremors, anorexia, and dilated pupils. More unpleasant and serious manifestations are fever, insomnia, emesis, diarrhea, and loss of weight.

Although the management of the abstinence syndrome is beyond the usual province of the general physician, there are rare occasions when he is faced with this problem as the result of definitive therapy in malignancy. Obviously the best treatment is to prevent addiction. In actual practice, however, the best that can be done is to delay or diminish the emergence of tolerance, as previously described. Bifrontal leu-
kotomy (Chap. III) will affect the abstinence syndrome. The narcotic antagonists (nalorphine and levallorphan) are of no value; indeed, if they are given to an addict, they will provoke violent symptoms of abstinence. The clinical management of the syndrome is a highly specialized technique and reference should be made to the publications of Eddy, Isbell, Wikler, and Fraser of the U.S. Public Health Service. In general, a course consisting of rapid transference to drugs

which produce less severe abstinence is followed. For example if the patient is addicted to morphine methadone is first substituted, and it in turn may be followed by substitution with codeine. The general rule is to reduce the frequency, dose and potency of the drugs as rapidly as clinical considerations permit, at the same time providing symptomatic relief by the use of *nonaddicting* agents.

ADJUNCTS AND MISCELLANEOUS AGENTS

SEDATIVES

Sedation can be an important and useful adjunct in the management of pain. It is especially valuable in diminishing the fear of pain and altering the reaction to pain. With proper sedation it is often possible to reduce both the dose and the frequency of opiate administration. Although respiratory depression is not common after the usual sedative dose it must be remembered that the depressant effects of a barbiturate and an opiate are additive. There are many barbiturates with different characteristics, from which the physician can make his selection. A nonbarbiturate sedative, such as methypylon (Noludar), can be used to advantage in doses of 50–100 mg t.i.d. If sedatives are administered orally they should be given before opiate medication because of the delayed gastric emptying time that is produced by the narcotic analgetics. The barbiturates and other drugs may be em

ployed usefully for hypnosis. Narcotics should not be used to obtain a secondary effect such as sedation.

CHLORPROMAZINE

Chlorpromazine (Thorazine) has many applications in the management of malignancy. It has sedative but not hypnotic properties. It is a potent antiemetic and as such is useful with radiation or nitrogen mustard therapy and it can reduce the requirements for opiates. The usual oral dose to provide for a reduction in narcotics is 25 mg b.i.d. or 10 mg t.i.d. but the drug can also be administered by slow and deep intramuscular injection. It is important to reduce the narcotic dose as soon as chlorpromazine treatment is begun. A useful schedule is to give one half the usual dose of the opiate until the patient's response to the combined drugs can be evaluated, in some cases the narcotic requirement can be reduced to one quarter the original dose. Maintenance dosage of chlorpromazine and the opiate is determined by the patient's response.

Chlorpromazine should not be used in patients who have received large or unknown quantities of opiates, barbiturates or alcohol, and the occasional hypotensive effects of the drug may make its use undesirable in the presence of arteriosclerosis or cardiovascular disease. The sedative and hypotensive effects of chlorpromazine limit its use in ambulatory patients. The physician should be on the alert for signs of jaundice.

which has been reported to occur following the administration of chlorpromazine

COBRA VENOM

The mechanism by which cobra venom produces analgesia is uncertain. Although the literature contains favorable reports on its effectiveness, this drug has not received the wide acceptance that one might expect for a non narcotic agent. Cobra (*Naja*) venom solution is marketed in ampules containing 10 mouse units per ml. The usual dosage schedule is 2.5 units intramuscularly the first day and 5-10 units each succeeding day for one week. Since the analgetic action is delayed the drug should be used for one week before evaluating its effect. If the opiate dose cannot be reduced by that time, or if there is no evidence of analgetic effect, there is little to be gained by continuing the drug. If the cobra venom is effective 5-10 units 2-3 times a week will provide for maintenance of the analgetic effect. The usual reactions to cobra venom are nausea, emesis, diarrhea and pain at the site of the injection.

CHAPTER 2

Nerve Blocks for Pain in Malignancy

THE INTRACTABLE PAIN that may develop with carcinoma not only vexes but frequently taxes the resourcefulness of the physician. The analgetic drugs are usually resorted to but invariably, a point of diminishing returns is reached. Drugs may literally be poured into a patient without producing the hoped for relief. An answer to this problem of pain may be found in nerve blocks. It is not the perfect answer, yet it may mitigate a seemingly hopeless situation.

PRINCIPLES OF NERVE BLOCKING

When performing blocks it will be well for the operator to know the principles essential to the proper execution of a nerve block for pain in carcinoma or of nerve blocks in general. He should have

1. An understanding of pain mechanisms in carcinoma
2. A knowledge of the anatomy of pain pathways

- 3 Familiarity with block techniques and blocking agents
- 4 Special instruments or procedures that will help increase or evaluate the success of a block
- 5 Patience

1 An understanding of the *mechanisms* or pathologic physiology of pain in carcinoma is necessary for the successful prosecution of an effective nerve block. These mechanisms are quite varied. If a hollow viscus is involved eventual obstruction with consequent *distention* will cause pain. In addition the distention can cause obstruction to the blood supply of the area involved giving rise to local hypoxia and more pain. Such pain perpetuates itself by causing reflex vasoconstriction—vasoconstrictor impulses propagated along the efferent sympathetic arm of the autonomic nervous system. Interestingly enough visceral pain impulses which are normally somatic are conveyed by nerve fibers that travel with the sympathetic nervous system. The neuron is found in the dorsal root ganglion. If on the other hand a solid viscus is involved, distention of its capsule or serosa may or may not cause any pain. As the tumor grows it encroaches on contiguous areas and may provoke pain in many different ways. It may by its mass exert *pressure on adjacent viscera* and cause pain. It may *invade nerve roots and other nerve structures*. It may *invade blood vessels and erode them*. It may *cause obstruction of blood vessels to a distal structure* and produce hypoxia and pain. It may *invade periosteum and bone, even to the extent of fracture*. The fractured bone may in

turn affect nerve roots or other nervous structures. The tumor may grow into joints and their capsules giving rise to an arthritis like pain. Finally, it may metastasize and produce pain distant to the principal site but necessarily following the patterns mentioned above.

2. A knowledge of the peripheral arm of the perception pathways and their points of accessibility is necessary for the effective performance of blocks. Briefly, pain sensation as perceived by receptors in various organs and structures of the body travels along well defined nerve pathways. These are either the peripheral mixed somatic nerves or the autonomic nerve plexuses. An outstanding fact which must be appreciated is that all nerve structures conveying pain have their primary neuron in the dorsal root ganglion. The somatic nerves may thus be blocked along their course—that is by means of an intercostal paravertebral, epidural or spinal nerve block. The cranial nerves and the autonomic ganglia associated with them may best be approached at their points of exit from the various foramina of the skull. The autonomic nerve plexuses may be attacked in the prevertebral area (for example splanchnic block) or in the paravertebral areas—lumbar, thoracic or cervical.

3. Skill and familiarity with the block technique increase the success of the procedure. Although skill may be considered essential, lack of it should not be construed as a deterrent to the uninitiated, since skill in this field may be acquired by frequent actual performance under good supervision. Familiarity and skill imply an adequate knowledge of the anatomic loca-

tion of the nerve or plexus to be blocked and the utilization of bony landmarks which can help greatly in the proper placement of a block needle. Familiarity and skill also assure the proper positioning of the patient. In the improperly positioned patient, important landmarks may be obscured and the accessibility of a nerve may be diminished. Familiarity also implies the availability of equipment in excellent working condition. The use of needles with snagged or dull points is an unconscionable practice which is to be deprecated.

4. Certain special procedures can help evaluate or increase the success of a block. The simplest proof of whether a nerve block is effective or not lies in the relief of pain in the area of distribution of the nerve and the development of parasthesia or analgesia in the same site. This is true of somatic nerves. One must remain aware, however, of the fact that fear and apprehension occasionally provoke an alarm reaction which develops a state of numbness or analgesia in the patient. Such a condition may be misleading in the interpretation of the outcome of a block. The blocking of any portion of the sympathetic nervous system may give rise to definite syndromes. An outstanding example of this is Horner's syndrome which develops after a stellate ganglion block; it usually consists of miosis, relative enophthalmos, ptosis, conjunctival injection, dryness of the face and stuffiness of the nostril on the ipsilateral side. The determination of skin temperatures before and after a block of sympathetic ganglia, especially if compared with the op-

Sup som aff	--
Deep som aff	-----
Visceral eff	
Visceral aff	----

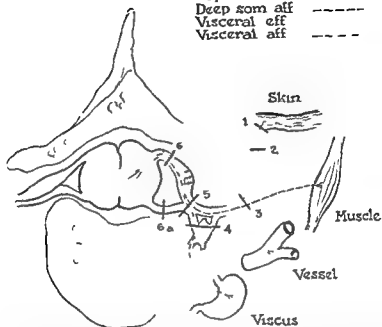


FIG 1—Peripheral pathways for pain and possible sites where they may be blocked 1 infiltration block intradermally and subcutaneously 2 field block 3 somatic nerve block 4 autonomic ganglion block 5 somatic paravertebral or epidural block ■ and 6a intrathecal or spinal block (Figs 1 5 6 7 and 10 from *S Clin North America* 35 9 1955 courtesy of W B Saunders Company)

posite side may prove very helpful One of the most useful tools in the performance of therapeutic blocks is the x ray By means of it, the localization and placement of a needle point is greatly simplified And the use of a contrast solution like Diodrast (iodopyracet) after the block needle has been placed is valuable in

predicting the spread of any solution that may be instilled through the needle. It is judicious to employ x ray localization and evaluation of spread with Diodrast (after a test for sensitivity) before injecting a neurolytic solution like absolute alcohol or 6-10 per cent phenol.

5. Aside from the requisite knowledge of the pharmacology of the different agents used in the performance of blocks, patience is both a virtue and a valuable asset which sustains the physician in his moments of frustration in this type of work. With patience, rapport may be established with the patient, and confidence gained. Such a relationship seems to augment the efficacy of a block.

DIFFERENT TYPES OF BLOCKS AND TECHNIQUES

Nerve blocks are limited to the accessible peripheral nerve trunks extending all the way from the proximal radicular portion where they lie freely in the spinal canal in the peridural space, in the paravertebral area and along their course into their terminal branches (Fig. 1).

INTRATHECAL NERVE BLOCK

The instillation of a local anesthetic into the subarachnoid space has long been employed to produce anesthesia for surgical procedures. The effects of a small amount of local anesthetic introduced into the intrathecal space are quite profound. In view of the marked analgesia which develops, one might state that this type of regional block is almost ideal as a

method for the interruption of pain pathways Yet there are so many factors involved in the controllability of any solution instilled into the spinal canal that the value of this procedure in the management of pain in malignancy may be questioned To cite an instance a negligible amount of local anesthetic introduced into the lumbar area will, in addition to causing marked anesthesia affect the motor nerves so extensively as to cause profound paralysis In the management of pain paralysis may be undesirable unless it is already present Of course it is possible to employ a relatively weak anesthetic solution so as to spare the more highly myelinated motor roots It is also possible to control the degree of spread of solution to some extent, by instilling the drug through a catheter as in continuous spinal anesthesia The limitation of this method lies in the length of time the catheter may be left in the subarachnoid space without leading to serious complications such as meningitis or arachnoiditis or, for single dose spinals in the number of times the procedure may be repeated without developing the same complications

INTRATHECAL ALCOHOL

By a propitious combination of certain anatomical and physical factors it has been found possible to instill minute amounts of absolute alcohol into the spinal canal and selectively destroy sensory roots without affecting the motor roots to any great degree if at all The different factors that make this procedure practicable are

- 1 All the sensory roots are in the dorsal position
- 2 All pain fibers have their primary neuron in the dorsal root ganglion, and so they must essentially run through the dorsal root in their course to the posterior horn
- 3 Absolute alcohol is hypobaric, that is it has a specific gravity of 0.810 as compared to spinal fluid which has an average specific gravity of 1.007. Alcohol will therefore float in spinal fluid
- 4 The spinal cord is more or less fixed in position and is anchored to the dura anteriorly by the dentate ligaments

Considering all these facts it is obvious that it is possible to introduce small amounts of absolute alcohol very carefully into the spinal canal without involving the spinal cord itself, the motor roots and the sympathetic fibers that run in them by way of the white rami communicantes. Going one step farther, the spinal canal may be placed in such a position that only the posterior roots of one side and a small segment thereof may be affected (Fig. 2).

The method of performing the intrathecal alcohol block is quite simple and is nothing more than a modification of the usual technic of introducing a spinal needle into the intrathecal space. The position of the patient is very important. The spinal segment and the posterior roots involved in the pain pattern are determined first. The patient is placed on an operating table which can be made to assume various positions and he lies prone with the segment to be blocked in the highest position. In other words, if the spinal

segment is between T5 and T8 on the right side this area is elevated by having the patient lie prone with this thoracic segment over the "break" or the kidney rest of the table. Sandbags or pillows may be employed to accentuate the scoliosis so that the head the



FIG 2 -Position of patient for intrathecal alcohol injection. Upper sketch shows distribution of alcohol affecting posterior roots only.

neck and the rest of the body are below the elevated segment. The table is then tilted so that the side of the body to be blocked (the right side) is higher than the other side without the body actually assuming a completely lateral position. Bonica figures this angle to be about 45 degrees. The patient is fixed or "strapped down" in this position to minimize inadvertent

ent movements which may cause the alcohol to spread to contiguous areas. Since the patient will have to stay in this position for at least 1-2 hours putting him to sleep may help relieve the discomfort of the situation.

A short beveled 22 gauge spinal needle is employed to perform the puncture. Once the resistance of the ligamentum flavum is felt the stylet is removed and a drop of local anesthetic or normal saline is placed on the hub. The needle is gently pushed in until the epidural space is reached this is indicated by the sucking in of the drop in the hub of the needle. An empty 2 cc syringe is now placed on the hub of the spinal needle and gentle traction maintained on the plunger as the needle is pushed forward slowly. By this method as soon as the dura is penetrated, spinal fluid is aspirated into the syringe and the needle is stopped at this point. It is necessary to make certain that the bevel of the needle is just within the dura. This may be accomplished by exerting gentle traction on the plunger of the syringe and pulling back the needle once more until no spinal fluid returns which signifies that the needle point is just out of the dura and then pushing the needle in again slowly until aspiration of spinal fluid just becomes possible. Then the alcohol is instilled. At the most 0.2-0.75 cc of absolute alcohol may be used. The smaller the volume the less the possibility of causing complications. An average of 0.5 cc is employed. A dry 2 cc syringe with markings showing 0.1 cc per line may be employed. Or if greater precision is desired a tuberculin syringe may be used instead. (Emphasis is made on the use

of a dry syringe since it is a little difficult to draw alcohol with a wet syringe) The alcohol is injected very slowly at a rate of not more than 0.1 cc per minute. The patient must be warned beforehand that, as the alcohol is instilled a sensation of warmth and severe pain will be experienced over the dermatomes to be blocked. He is cautioned not to move at all during this period and is informed that this sensation is momentary.

Following the injection of the alcohol the patient is left in this same position for at least 1-2 hours after which he may be turned into the supine position. It is preferable to have the patient lying in bed for the next 12-24 hours. The effects are immediately apparent if successful although a few days later the patient may experience a sensation of hyperalgesia or hyperesthesia this usually disappears. A disconcerting "burning" sensation may develop which may be relieved by paravertebral sympathetic block.

Complications may arise occasionally depending on the site of the injection. In the lumbar area for example it is not uncommon to find weakness of an extremity or paralysis of the sphincter of the bladder and rectum. In the neck and upper thoracic areas weakness of an upper extremity may develop. Such weakness or sphincter paralysis disappears after a period of 3-6 weeks.

The intrathecal alcohol block is probably most useful in patients who are not physically capable of withstanding a neurosurgical procedure for the interruption of pain pathways. The block may be repeated

without necessarily causing any serious complications. In fact, if an extensive area is involved in the pain pattern it may be wise to block off small segments at a time. If both sides are afflicted one side may be blocked first and the other side treated after an interval of a week. A trial block with a local anesthetic like hypobaric pontocaine (tetracaine) might be utilized before alcohol is used, in order to acquaint the patient with the analgesia that develops. Hypobaric pontocaine is a solution containing 1 mg per cc of distilled water and having a specific gravity of 1.003.

A 27 year old woman was referred to the anesthesia department complaining of pain radiating to both lower extremities but more severe on the left side. She had had an abdominoperineal resection for carcinoma of the rectum. Despite the extensive resection metastases had apparently extended to the sacral area probably involving parts of the lumbosacral plexus of nerves. She had had a colostomy and an indwelling urethral catheter had been introduced. In view of her poor physical condition and what was felt to be a terminal state of the disease an intrathecal alcohol block to the left lower extremity was first decided on. A trial injection of hypobaric pontocaine was made to familiarize the patient with the effects of the block. She was placed in the prone position with the left lumbar area uppermost for the alcohol injection. Absolute alcohol 0.5 cc was instilled, the introduction of the entire amount taking about 11 minutes. Relief of pain was immediate and complete. The following complications were noted: weakness of the left lower extremity and a burning sensation radiating down the left leg. The burning pain was suggestive of a sympathetic type of pain. A week later a paravertebral block of 1, 2, 3 sympathetic ganglia was performed using 6 per cent phenol. The burning pain was completely

relieved Intrathecal alcohol block to the right side was contemplated but it was decided to wait for the disappearance of paresis of the left leg. However the patient developed metastases in the lungs and died before the right side could be blocked.

The subarachnoid injection of alcohol is considered a major procedure and should be done in the operating room. In spite of the seeming simplicity of the method serious complications may develop from the bungling efforts of the uninitiated. No one should attempt this procedure without being thoroughly familiar with the technical and physiologic details as associated with the administration of a spinal block.

EPIDURAL BLOCK

The epidural space is a potential cavity limited cephalically by that portion of the base of the skull to which the dura is anchored, laterally by the intervertebral foramina anteriorly by the body of the vertebrae and caudally by the sacrum and its openings. Any solution instilled into this potential cavity will thus tend to follow the path of least resistance and spread in a cephalad and a caudad direction and laterally following the intercostal nerves. It is difficult to control the spread of any solution introduced into this space, and the introduction of necrotizing solutions may therefore be dangerous, inasmuch as large volumes are necessary to be effective and small volumes may be futile.

The epidural block is of limited value in the man

agement of pain in malignancy In terminal stages of the disease it is possible to introduce a catheter into the epidural area and inject local anesthetic solutions at intervals of four to eight hours and thereby relieve pain Granulation tissue develops around the tip of the catheter and plugs it within a period of 48-72 hours so another catheter may have to be inserted Considerable relief of pain may be afforded the patient in this manner, but prolonged use of the epidural catheter is impractical since the continuous presence of this foreign body encourages the development of infection along the path of the catheter

PERIPHERAL NERVE BLOCKS

As previously stated nerves may be attacked along their course from their point of exit to the periphery Anatomically and physiologically most peripheral nerves are mixed nerves (motor and sensory) and blocking them interferes with their motor function In certain areas of the body, some major nerves are predominantly sensory, like the trigeminal (5th cranial nerve) If mixed and blocked the motor activity that normally results from the influence of the motor fibers may be carried on by neighboring structures (for example intercostal nerves) Another anatomic fact of importance is that the bony landmarks are valuable in locating these nerves X ray examination may prove very useful in determining whether the needle point is in close proximity to the nerve in relation to the bony landmarks

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reflex vasoconstriction furthering the hypoxia. Relief may be obtained by interrupting vasoconstrictor fibers in the sympathetic system. Lastly sympathetic plexuses and ganglia are very accessible and quite vulnerable to mild necrotizing agents considering their poor myelin covering.

AGENTS USED FOR BLOCKS

There are two main groups of agents employed in performing blocks for pain of malignancy: (1) local anesthetic agents and (2) nerve necrotizing agents.

LOCAL ANESTHETIC AGENTS

The local anesthetic drugs available are so numerous that one is frequently faced with the problem of selecting one agent from among several that may be equally good. Final choice, however, is frequently dictated by certain criteria referable to the drug, such as: (a) rapid onset of action, (b) low toxicity, (c) long duration of action, (d) nonirritation of tissues, (e) profound analgesia, and (f) selectivity of effect. Other factors, referable to the physician employing the drug, must also be considered—for example: (1) familiarity with the drug, (2) availability of drug, (3) cost of drug (must be relatively cheap), and (4) a prejudicial preference for the agent. Not all the criteria referable to the drug can be satisfied by any one agent, but a combination of two or three drugs may satisfy all or most of them. For instance, mixing 0.25 per

The cranial nerves may be blocked at their point of exit from the foramina at the base of the skull. The intercostal nerves may be blocked paravertebrally as they emerge from the intervertebral foramina at the angle of the ribs posteriorly between the line joining the midline vertebral spines and the medial border of the scapula or at the posterior axillary line. The cervical nerves are vulnerable as they wind anteriorly over the transverse processes. Blocking the spinal nerves in the paravertebral area, however may involve certain dangers and complications. It is not too difficult to introduce the anesthetic agent into the subarachnoid space by inserting the tip of the needle into a dural sleeve or as Moore has shown injecting directly into the nerve through the epineurium enabling the drug to find a passage into the intrathecal canal. But a necrotizing agent inadvertently introduced into the spinal canal may cause serious complications such as arachnoiditis or transverse myelitis with a concomitant paralysis.

SYMPATHETIC NERVE BLOCKS

The sympathetic nerve block may prove useful in the control of pain referable to a viscus. As mentioned previously pain fibers from most visceral organs travel by way of the sympathetic plexuses and ganglia but do not necessarily form synaptic connections. Accordingly, visceral pain fibers may readily be interrupted by a sympathetic block. The other mechanism of pain in a viscus is distention which causes hypoxia and

NERVE NECROTIZING AGENTS

These agents exert their effect by destroying the nerve fiber or the cell. It has been established that necrosis of the nerve fiber extends all the way back to the first node of Ranvier. The nerve cell of a somatic nerve may remain intact, thus implying that regeneration of the nerve fiber is not an impossibility. The relief afforded by these agents is therefore only relatively permanent. Three agents have been outstanding: ethyl alcohol, phenol and ammonium sulfate. Ethyl alcohol has been employed in concentrations varying from 50 per cent to absolute. The best concentration to use is the absolute alcohol because lower concentrations tend to give unpredictable results. Although the incidence of neuritis is high after a block with ethyl alcohol, the results when successful are so gratifying that the risk is considered worthwhile. Ethyl alcohol has a very limited degree of spread in the tissues. Experimentally 5 cc of alcohol injected into muscular tissue will cause a necrosis 1 cm in diameter. If injected into a fascial plane of course the spread may be greater and may follow the course of a nerve. Partial or incomplete relief of pain after an alcohol block may be ascribed to improper placement of the needle, use of an insufficient amount of alcohol or dilution of the alcohol by the previously instilled local anesthetic agent. Phenol (6 per cent) acts very well on sympathetic nerves and it may be employed in greater volumes than alcohol. Higher concentrations of phenol up to 10 per cent may be employed if the solution is

cent pontocaine with 2 per cent procaine will give an agent that is rapid in onset (due to procaine) and has low toxicity, profound analgesia and relatively long duration of action. It may have a poor selectivity of action in that it indiscriminately affects motor, sensory and sympathetic nerves, but it satisfies most of the factors referable to the physician employing the drug. Prejudicial preference for a local anesthetic agent may exert an unduly large influence in the selection of the agent to be employed.

The value of local anesthetic agents in malignancy lies in their usability for differential diagnosis. Depending on the concentration of the drug or the placement of the needle it may be possible to establish whether somatic sensory pathways or sympathetic pathways or both are involved and by means of local anesthetics it may be possible to determine which or how many of the sensory nerves supplying an affected area are involved. Repeated blocks with local anesthetic agents at regular intervals may diminish the pain considerably. This may also be accomplished by introducing a plastic catheter in the immediate vicinity of the nervous structure to be blocked. During the performance of an alcohol block the previous instillation of a local anesthetic agent mitigates the intense pain associated with the introduction of alcohol into the tissues, as well as the pain from the insertion of the block needle itself. A preliminary local anesthetic block of the nerves to a painful area enables the patient to evaluate the loss of sensation that may develop with a more permanent type of block.

(5th cranial) nerve Interruption of any of the three divisions of this nerve—mandibular, maxillary and ophthalmic—as they emerge from their respective foramina at the base of the skull will control pain from these regions If all three divisions are involved, a gasserian ganglion block may be the method of choice Injection into the gasserian ganglion implies interruption of all three divisions of the 5th nerve, so that the ophthalmic division which supplies all sensory elements of the area around the eye and the eye itself is affected A serious complication of this procedure is keratitis and even ulceration of the cornea Where life expectancy is not too long such a complication may not be too great a price to pay for the ensuing relief of pain In occasional instances when the eye is involved, a block of the ophthalmic division or the gasserian ganglion may be done with relative impunity

A 67 year old man with an invasive slow growing epidermoid carcinoma of the face which had completely involved the left eye and its socket was brought to the operating room for excision of the metastatic growth invading the eye socket The chief complaint was severe pain in this area During the procedure the opinion of the anesthesiologist was solicited for whatever extra procedure might be performed to alleviate the pain Extensive excavation of the left eye socket had been performed and closer scrutiny disclosed the ready accessibility of the gasserian ganglion Injection of absolute alcohol into the area of the gasserian ganglion was advised and subsequently performed Relief of pain was complete

Tumors may also arise from the paranasal sinuses Again pain develops as a consequence of compression

warmed in order to increase the solubility of the phenol. As much as 20-25 cc of 6 per cent phenol has been instilled in the splanchnic area for a celiac plexus block. Even though sympathetic nerves are very vulnerable to necrotizing agents, they regrow so fast that phenol instillation may have to be repeated more frequently than alcohol instillation. Ammonium sulfate has been used most frequently in concentrations of 0.75-2.0 per cent. This agent was thought to have a selective action on somatic sensory nerves, but it has not come up to expectations. A concentration of 6 per cent is believed to be more effective.

Whenever these necrotizing agents are employed, it is wise to use x rays to help localize the site of the needle point and, if possible, to instill a contrast solution like Diodrast prior to instillation of alcohol or phenol in order to be able to predict the spread of these agents.

BLOCKS FOR DIFFERENT REGIONS

HEAD AND NECK

Malignant growths frequently involve the different structures of the face, the mouth and its contained organs, the neck and the throat. Pain results from pressure on sensory nerve structures or involvement of the nerve structures themselves. In the facial area, tumors may develop from the skin, especially around the mouth and nose, or from the sinuses in the paranasal area. Pain impulses from this area are mediated through the three main divisions of the trigeminal

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or of actual involvement of branches of the trigeminal nerve. Tumors in this area frequently affect the maxillary and the mandibular divisions. Blocks of these branches are easily accomplished where the branches emerge from their respective foramina. In blocking these divisions, paresthesias may be used to ascertain the position of the needle point. Instillation of 1-2 cc of a local anesthetic agent followed by development of anesthesia or analgesia over the facial segments supplied by these nerves offers some degree of reassurance of the proper position of the needle point. Three cc of absolute alcohol may then be instilled to produce a permanent block. In addition to utilizing paresthesias, x ray study is valuable in executing this type of block. With the head in the proper position, a good x ray picture diminishes the element of chance in placing the needle. It is quite simple to demonstrate the needle point close to or at the foramen rotundum for the maxillary nerve and the foramen ovale for the mandibular nerve (Fig 3).

Malignant tumors may also develop in the tongue, the buccal mucosa and the salivary glands. Tumors arising in the tongue occasionally pose a complex problem in pain control because the tongue is innervated by several nerves. The anterior two thirds of the tongue is innervated by the mandibular division of the 5th cranial nerve by way of its terminal branches—the lingual nerve. The posterior third is supplied by the glossopharyngeal nerve. Nerve twigs also come from the cervical plexus. Thus should the pain arise from a site common to both the trigeminal

and the glossopharyngeal nerves blocking both may be necessary to relieve the pain. If some pain persists after blocking both the 5th and the 9th cranial nerves it may be necessary to interrupt spinal nerves C2 and C3. Tumors of the mandible may of course give rise



FIG 3 —X ray of base of skull showing needle (A) with point close to foramen rotundum (B) for maxillary nerve block.

to pain referable to the mandibular division of the trigeminal nerve and to C2, C3 and possibly C4.

In discussing pain as a complication of malignant tumors of the face, mouth, paranasal sinuses and mandible, one frequently loses sight of the fact that after the malignant growth has been radically excised and possibly eliminated, grossly, pain may persist post

operatively. The misery provoked by this persistent pain may make the patient almost as unhappy as having the original tumor. Pain may also develop after irradiation of the tumor area or after radon seed implantation.

A 70 year old man had a tumor on the dorsum of the right half of the tongue. Apparently the tumor was of a low grade type of malignancy with no metastases to lymph nodes or contiguous structures. The tumor was excised and recovery from the operation was uneventful. However postoperative pain developed. The patient was referred to the anesthesia service and the following procedures performed. A lingual nerve block with tetracaine was performed to find out how much relief could be obtained. Relief of pain was immediate and considerable and lasted for about 48 hours. As a result an alcohol block was performed employing 2 cc of absolute alcohol. Relief was good but a burning type of pain developed on the dorsum of the tongue. Since it seemed that the nerve had been only partially destroyed by the alcohol instillation another injection of absolute alcohol was made in the area of the lingual nerve two weeks after the first injection but the burning pain persisted. The relief of the original knife like pain at the site of the incision lasted for a period of two months after which the pain returned. An extraoral mandibular nerve block was executed with 3 cc of absolute alcohol abolishing the pain at the site of the incision but leaving a soreness extending down the anterior third of the tongue and the buccal area. This distribution of pain was due to the lingual nerve.

year

from an extensive tumor
base of the tongue
irradiation therapy
Pain developed

over the irradiated area. It was burning in character and thought to be mediated through sympathetic pathways. A stellate ganglion block was performed and complete relief of pain was obtained. In view of this 8 cc of 6 per cent phenol was instilled into the region of the stellate ganglion under x ray control. Pain relief was not as complete as with the local anesthetic but at least 75 per cent relief was experienced.

In the neck and lower jaw pain developing from malignant tumors of the mandible, the submaxillary glands, the thyroid and the larynx may give rise to varying degrees of pain. For pain arising from the mandibular area a mandibular nerve block reinforced by injection of the deep cervical plexus (C2-3-4) will provide pain relief in most instances. For pain in the area of the neck a block of the deep cervical plexus will be satisfactory in most instances except for the larynx and the esophagus. These structures receive their sensory innervation from the vagus through the superior and inferior laryngeal nerves respectively. Any standard text on regional blocks will show that it is relatively easy to block the superior laryngeal nerve.

In the region of the neck extensive necrosis or radical surgery frequently defiles the area so extensively that landmarks necessary for the proper execution of the above-mentioned blocks may be obliterated. The instillation of absolute alcohol intrathecally may be valuable—in fact this may be the only means available for providing relief from pain in the terminal stage aside of course from massive doses of analgetics which may not be effective at all.

UPPER EXTREMITY

The brachial plexus which derives its origin from the anterior primary divisions of the spinal nerves C5, 6 7 8 and T1 supplies the chief innervation to the upper extremity Sympathetic innervation (post ganglionic fibers) comes from the stellate ganglion the middle cervical ganglion and paravertebral ganglia T2 3 and 4. Malignant tumors in the neck may involve the divisions and trunks of the brachial plexus and provoke severe pain referable to the upper extremity Tumors of the dome of the lung frequently involve the brachial plexus causing severe pain trophic changes in the arm and paresis or paralysis Aside from injecting absolute alcohol into the intrathecal space there is no satisfactory way of relieving pain in these patients Injection into the brachial plexus necessarily produces complete paralysis of the extremity even if analgesia is provided Some patients with pain arising from involvement of the brachial plexus feel that they should try to preserve whatever function remains in the extremity It is rather pathetic and difficult to convey to them that the situation is progressive and not static and that complete paralysis of the extremity will develop eventually A stellate ganglion block or block of T2 3 and 4 ganglia may diminish the pain to some extent This may be explained by improvement of the blood supply to the extremity through dilation of blood vessels thus relieving somewhat the hypoxic condition

THORAX

Tumors arising in the tracheobronchial tree and affecting the bronchus, esophagus other structures in the mediastinum or thoracic vertebrae often cause pain in the thoracic area. Relief of pain arising from involvement of the viscera in the thorax is rather unpredictable and complete relief is seldom obtained. This may probably be explained by the fact that thoracic visceral innervation is so inextricably complex that huge areas have to be blocked frequently to obtain any semblance of relief. All too often, one is tempted to ascribe all sensory thoracic visceral innervation to the sympathetic division of the autonomic nervous system although it is known that quite a number of the sensory fibers travel with the vagus. The relative inaccessibility of the plexuses in the thoracic cavity increases the difficulty of relieving pain arising from thoracic viscera. One mitigating factor is the fact that the cervical sympathetic ganglia contribute many fibers to the formation of the bronchial and cardiac plexuses especially the middle cervical and the stellate ganglia. These ganglia are situated where they are readily accessible to the block needle. The other factor is that the vagus nerve as it emerges at the base of the skull is quite vulnerable. As far as intrathoracic viscera are concerned pain arising from these structures may be relieved by blocking the sympathetic ganglia the vagus nerves or both. The upper parts of the esophagus and the tracheo

UPPER EXTREMITY

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pect of the trachea and the vertebral body—that is, between the trachea and the artery. Bony contact is established with the transverse process of the 7th cervical vertebra in most instances. After making sure by aspiration that a vessel has not been entered, the

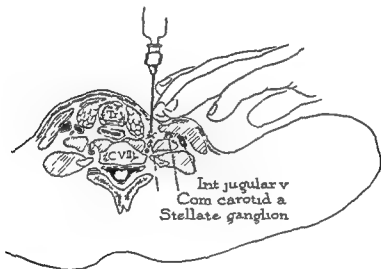


FIG 4—Anterior approach for performance of stellate ganglion block

local anesthetic solution is injected. Five to 10 cc of local anesthetic solution is sufficient to produce a block of the ganglion by diffusion. By this approach the needle point is usually introduced into the same fascial plane as the stellate ganglion. The appearance of Horner's syndrome—miosis, ptosis, conjunctival injection and relative enophthalmos—assures the proper placement of the needle point. There is also dryness

bronchial tree receive fibers from the stellate and middle cervical ganglia and the upper three or four thoracic ganglia

STELLATE GANGLION BLOCK—The stellate ganglion may be blocked by any of *four* approaches. It may be approached from the *posterior* aspect; this is very similar to performing a paravertebral block. This method is not very popular, and the danger of penetrating a projecting dural sleeve along the cervical spinal nerve is ever present. The ganglion may be approached from the *lateral* aspect of the neck. The needle point is directed to contact the body of the 7th cervical vertebra or the 1st thoracic vertebra. The lateral approach always seems to be quite formidable in view of the number of structures that intervene as the block needle traverses the region between the skin on the lateral aspect of the neck and the body of the 7th cervical vertebra, and this approach has lost its popularity. Volpitta and Rusteen modified this procedure by advocating an *anterolateral* approach which is quite similar to the lateral approach except that it utilizes more landmarks. The most popular method of performing the stellate ganglion block is by way of the *anterior approach*.

In the anterior approach (Fig 4) on a point located 1-1½ in above the space of Burns, the index finger is insinuated between the trachea and the sternocleidomastoid muscle on the side to be blocked at the same time feeling for the carotid artery. The trachea is pushed medially and the carotid artery more or less laterally. The needle is inserted along the lateral as

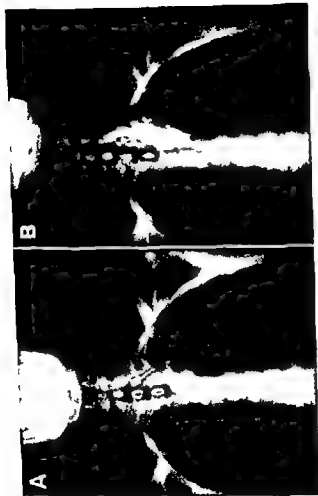


FIG 5—A stellate ganglion block with needle point on transverse process of T2 B same block after injection of Diodrast showing cephalad spread sufficient to block stellate The needle placement in this block was unnecessarily low However the objective was to try to catch the sympathetic components of T3 and T4 with one block in this patient who had a causalgia of left arm Six per cent phenol gave complete relief

of the face on the side blocked and stuffiness of the nose. It is interesting to note a patient perspiring only on the contralateral side after a stellate ganglion block.

If a stellate ganglion block relieves pain in the head and neck area, the upper extremity or the upper thoracic area, a necrotizing agent should be instilled to provide for a longer duration of relief. Absolute alcohol may be employed. However, experience has shown that 6 per cent phenol provides a very satisfactory agent for necrotizing the stellate or any sympathetic ganglion since it does not provoke as much irritation as absolute alcohol. Thus relatively larger amounts of phenol solution may be instilled in the region of the stellate ganglion providing for a greater margin of success. As previously mentioned, x-rays should be utilized in localizing the placement of the needle point and predicting the spread of solution by instilling Diodrast into the area to be blocked (Figs 5 and 6). As much as 10 cc of 8 per cent phenol has been instilled into the area of the stellate ganglion without causing any apparent damage to surrounding structures. The solution may spread from the immediate vicinity of the stellate ganglion along fascial planes to affect the middle cervical ganglion and caudally as low down as sympathetic ganglia T2 and T3.

As in any other block, complications develop occasionally. Rarely a pneumothorax occurs or an intrathecal injection is made by the anterior approach to the stellate ganglion. The carotid may be punctured though this is not any more serious than performing a carotid puncture deliberately for arteriography. The



FIG 7—A anteroposterior view of upper thoracic paravertebral blocks with needles in position
B oblique lateral view of same patient after injection of Diodrast solution

recurrent laryngeal nerve may be involved causing some amount of hoarseness. On the right side the esophagus may be affected and give rise to some dysphagia. Whenever phenol or alcohol is used to



FIG. 1—Stellate ganglion block with needle on C6. Lateral approach was used. Diodrast injection showed a cephalad spread to the middle cervical ganglion and a caudal spread down to T2.

cause necrosis of the stellate ganglion, the subsequent ptosis and miosis may persist for some time. Chemical lysis of a nerve or ganglion or plexus is not as permanent as one might be led to believe for nerves and ganglia regrow rapidly after chemical interruption.

A good indication of regrowth is recurrence of the original pain, and one should not hesitate to repeat the block with a neurolyzing agent whenever the pain occurs. The effects of a chemical sympathectomy may last from one week to as long as six months. If a surgical sympathectomy is attempted after a chemical sympathectomy the surgeon often has much difficulty in locating the sympathetic ganglion.

PARAVERTEBRAL SYMPATHETIC BLOCKS—To obtain relief of pain lower down in the thorax especially of the visceral paravertebral sympathetic blocks may have to be performed. The technic is relatively simple and was originally devised by Kappis. The approach is posterior and involves the introduction of the block needle on a point lateral to the midline by 1½–2 in opposite the intervertebral foramina. Actually some authorities prefer to raise the wheals opposite the vertebral spines 1–2 cm from the midline establish contact with the lamina and slide off the lamina into the intervertebral foramen. This approach has been found very successful in most instances.

A local anesthetic should always be employed first in blocks of this kind whenever a more permanent type of procedure is contemplated. The kind of local anesthetic to be used is beside the point. What is important is that the instillation of a local anesthetic gives an idea of how much relief may be obtained with the contemplated block and at the same time familiarizes the patient with the effects of a block. Occasionally repeated blocks with a local anesthetic may afford a considerable amount of relief of the pain.

block the nerve and viscera. A somatic nerve block in the thoracic area may have to be performed if a tumor has invaded the pleura or thoracic wall and is causing severe pain. In view of the extensive overlapping of spinal nerve distribution in the thoracic area, several of the nerves may have to be blocked. If for example the pain is confined definitely to T7, blocking T6 and T8 will give a greater degree of pain relief than just blocking T7. Where tumor tissue has invaded the spine involving the nerves as they come out of the dura a paravertebral block is definitely out of the question. The only procedure that may afford some relief aside from neurosurgery is probably intrathecal injection of absolute alcohol.

An aspect of thoracic pain in malignancy that should not be lost sight of is post thoracotomy pain. This condition is frequent and the patient may suffer as much from it as from the original malignant condition for which he was operated on. A paravertebral block of the nerves supplying the area of the incision may eliminate or mitigate the pain.

INTERCOSTAL NERVE BLOCK—The value of this type of block is limited. If the pain is confined to the anterior aspect of the chest and is superficial or can be demonstrated to affect the thoracic wall predominantly this block may be useful. The intercostal nerve block is easily performed. It may be done posteriorly at the angle of the ribs at the posterior axillary line or at the midaxillary line. Occasionally, where the pain is confined to the sternal area the block may be done at the anterior axillary line.

picture In most instances, the patient complains of being numb and sore over the same area Numerous remedies for the neuritis have been suggested, such as reblocking the affected nerve, although the original block was intended only for the sympathetic ganglion Some authors have suggested instilling procaine after the alcohol block before pulling out the needle, others have given procaine or pontocaine by intravenous drip to relieve the pain (1 Gm procaine in a 0.2 per cent solution)

It is possible inadvertently to enter a prolonged dural cuff causing instillation of a necrotizing agent into the spinal canal A Brown Sequard type of paralysis has been reported Therefore it is wise to have the patient lie on his side after instillation of a necrotizing agent in case some of it may have been introduced into the intrathecal space Because alcohol is hypobaric and will float in spinal fluid, it affects only the radicles in the uppermost portion should it enter the subarachnoid space Similarly most local anesthetics employed for blocks are usually hypobaric In performing paravertebral blocks, therefore the area to be blocked should be situated superiorly so that any anesthetic agent injected into the subarachnoid space accidentally during a paravertebral block will be confined to the upper portion of the spinal canal and thus affect only the rootlets in that area

Anatomically, the somatic nerve in the thoracic area is located very close to the ganglion as it lies in the intervertebral foramen It is obvious as was pointed out previously that a block of the ganglion may also

the breast. A type of pain frequently seen in the thoracic area is that which follows radical mastectomy and is confined to the axillary region in most instances. Pain may be relieved by a paravertebral block or an intercostal nerve block of spinal nerve T2 at the posterior angle.

EPIDURAL NERVE BLOCK—Occasionally severe pain referable to the thoracic wall may be so extensive as to render paravertebral and intercostal blocks impractical. An *indwelling catheter* introduced into the epidural space may help considerably in controlling such a wide area of pain as this. In the terminal patient suffering intensely from severe pain over a wide area the indwelling epidural catheter may be very valuable in relieving pain. Local anesthetic solutions may thus be injected at regular intervals. The volume of anesthetic agent employed depends on the size of the area involved and the resistance that the patient may develop to the drug.

ABDOMEN

Pain fibers from the abdominal viscera travel by way of the sympathetic nervous system although the primary neuron lies in the posterior root ganglion (see Fig. 1). Therefore visceral pain from the abdomen may be relieved by interrupting sympathetic pathways by means of paravertebral blocks in the thoracic area or by a splanchnic block.

SPLANCHNIC BLOCK.—This term is probably a misnomer since there are three splanchnic nerves—a

The intercostal nerve is located all the way along its course from the intervertebral foramen to the sternal edge anteriorly under the inferior border of the rib. The bony rib is therefore the chief landmark in performing this block. The outer surface of the rib is contacted with the point of the needle preferably at the posterior angle. The needle is then made to slide over the lower border of the rib and the solution instilled. In obese individuals the posterior angle of the rib may be hard to palpate making the block a little more difficult to perform. Under such conditions it is preferable to make the block at the posterior axillary line. Three to 5 cc of solution is enough to anesthetize the nerve. The incidence of neuritis after the instillation of a necrotizing agent into the region of the intercostal nerve is quite high. Aside from this complication the pleural cavity may be entered and the lung punctured causing a pneumothorax. However such a complication is not too serious provided the patient is kept quiet in bed. The air in the thoracic cavity is eventually absorbed and the pleural tear sealed off. Occasionally a tension pneumothorax may develop in which case the air may have to be evacuated. An 18 gauge needle attached to a three way stopcock and a 20 cc syringe are sufficient to accomplish this procedure.

Malignant tumors of the thoracic cage provoking pain are probably not too frequent. They may be invading growths from tumors of intrathoracic viscera or tumors arising from the bony cage or occasionally invasion of the thoracic wall by malignant tumors of

If the back is broad or the 12th rib is not palpable the spine of the 1st lumbar vertebra is located and a point 2-3 in lateral to it is used as the point of insertion. The block is best performed with the patient

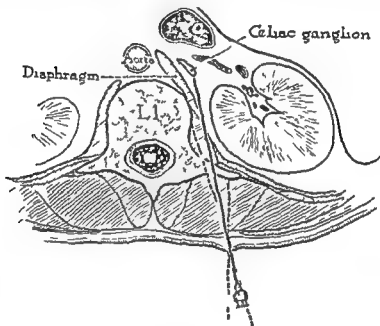


FIG. 8—Cross section at L1 showing needle point in vicinity of celiac ganglion

lying in the lateral or the prone position. As soon as the point of insertion has been decided on a skin wheal is raised at this site and the block needle is introduced at an angle of about 30 degrees to the median sagittal plane at the same time aiming for the body of the 1st lumbar vertebra. Frequently the

greater, a lesser and a least splanchnic nerve. What is significant is that all three traverse the largest sympathetic plexus in the body, known as the celiac or solar plexus. Aside from the splanchnic nerves the vagi especially the right vagus send branches to it. The celiac plexus is located at the upper border of the first lumbar vertebra and is intimately related with the celiac and superior mesenteric arteries. Actually therefore a splanchnic block, as performed, is more a celiac plexus block than anything else. A good celiac plexus block will interrupt most intra abdominal visceral pain pathways (Fig 8).

There are two outstanding approaches to the splanchnic plexus—anterior and posterior. The *anterior approach* necessitates entry into the abdominal cavity and is best performed by the surgeon during the course of the operative procedure. It was first advocated by Braun and involves injecting a local anesthetic into the region of the 1st lumbar vertebra between the inferior vena cava and the abdominal aorta.

The *posterior approach* was developed by Kappis and obviously entry into the abdominal cavity is not a requisite. The landmarks are the 12th rib, the spine of the 1st lumbar vertebra and the transverse process of the 1st lumbar vertebra. Depending on the breadth of the patient's back, any one of two points may be utilized as the site of insertion of the long (6 in.) block needle that is employed. If the patient's back is rather narrow and the 12th rib easily palpable this rib is a good landmark, and its inferior border may be used as the point for inserting the needle.

provokes is much less than with absolute alcohol. As much as 30 cc of 8 per cent phenol has been employed at one time. For psychologic reasons it may be best to perform the block on the side presenting



FIG 11—A anteroposterior view showing needle point at lower border of T12 and Diodrast spread from T11 to L2
B lateral view of same injection

the most pain. If pain still persists on the other side a splanchnic or celiac plexus block may be done after an interval of one week.

The scope of the celiac plexus block is extensive. It may relieve pain caused by malignant tumors of

transverse process of the 1st lumbar vertebra may be encountered in transit. If so, the needle is redirected either cephalad or caudad to bypass the process. As soon as contact with the body of the 1st lumbar vertebra is established, the needle is withdrawn and redirected at a more acute angle in relation to the median vertical plane, until the vertebral body is again contacted. This procedure is repeated until the needle point is felt to slide off the bone. As soon as bony contact is lost, the point of the needle is most probably in the same fascial plane as the celiac plexus.

The solution may then be instilled into the area. If a permanent type of block is contemplated, x-rays should be used. Films in both the anteroposterior and lateral positions should be taken after placement of the needle (Fig. 9). If the needle point is in good position, Diodrast should be instilled to predict the spread of the necrotizing agent. Diodrast may be mixed in equal amounts with a local anesthetic agent and used as such. This will diminish the concentration of Diodrast and may lessen the chances of a reaction to Diodrast. The amount of Diodrast solution employed should approximate the amount of necrotizing agent to be injected into the area, the average amount employed is 10 cc. If the spread of the Diodrast solution is satisfactory, the neurolytic agent may be introduced. It is advisable to wait 10-20 minutes in order to assure absorption of the Diodrast. Six per cent phenol, the preferred necrotizing agent, works very satisfactorily on sympathetic nerves and ganglia, and the amount of neuritic phenomena it

the pancreas liver stomach, duodenum small bowel mesentery and other upper abdominal structures but the relief afforded is unpredictable Depending most probably on how much of the plexus is affected by the agent, the relief may last anywhere from a week to a year

A man 65 had an inoperable carcinoma of the stomach with metastases to the liver Gastrostomy was performed The patient complained of continuous, unrelenting pain in the epigastric area A splanchnic block was performed eliminating 80-90 per cent of the pain It improved his appetite allowing him to gain 5-10 pounds The relief of pain was good until his death

A woman 45 had a pancreatic tumor which was not resectable She complained of a continuous epigastric pain confined chiefly to the right side A splanchnic block was performed under x ray visualization using 12 cc of 6 per cent phenol Relief of pain lasted for one week The impression was gained that an insufficient amount of phenol was employed

Despite the seeming simplicity of the celiac plexus block, complications may develop A too cephalad placement of the needle point may find it within the thoracic cavity occasionally causing pneumothorax and it is possible to puncture the inferior vena cava or the aorta Such complications as these however are not too serious In transit to the body of the vertebra the needle may impale the kidney or the pelvis of the kidney may be penetrated The needle may find its way into the abdominal cavity which happens occasionally without necessarily causing frank



FIG 10—A bilateral paravertebral sympathetic block with needles in position—body of L2 ■ after injection of Diodrast, the solution spread one segment above to L1 on the right and was more or less confined to L2 on the left

intended to interrupt nervous pathways to deep pelvic organs may seriously interfere with the motor functions of the lower extremities. In a relative manner, it is anatomically fortunate that visceral pain fibers frequently travel by way of the sympathetic ganglia and plexuses. Thus in the lumbar region, the sympathetic ganglia and the paravertebral plexuses are readily accessible. In the deep pelvic region especially the sacral area some portions of the sympathetic nervous system become almost inaccessible, or if they are accessible they may be very intimately associated with somatic motor and sensory nerves to the lower extremity.

In view of the difficulty of dissociating pain pathways from important motor nerves in the pelvic area, it may be much wiser in the fairly good surgical risk patient, to perform a neurosurgical interruption of pain pathways in the cord or higher up in the central nervous system.

Occasionally pain may be confined to one side. If the pain is visceral in nature—that is poorly defined or cramplike—and assuming that there is no evidence of severe bowel obstruction a sympathetic block to that side may be performed.

LUMBAR PARAVERTEBRAL SYMPATHETIC BLOCK.—In performing this type of block one anatomical consideration should be kept in mind. In the lumbar area the sympathetic ganglia assume a more ventral position on the vertebral body as compared with the lateral situation of the thoracic sympathetic ganglia in the intervertebral foramen. Thus, the approach is

complications and the possibility of invading the intrathecal area or penetrating into a projecting dural sleeve is not too remote. In addition infection may develop along the course of the needle. Antibiotics should be administered routinely to patients to minimize infection.

Intercostal blocks are of little value in abdominal visceral pain. They may prove useful as in the chest for painful tumors of the abdominal wall or in the control of referred pain which is seldom seen in cases of pain in malignancy. Again as in the thoracic cavity an indwelling catheter in the epidural space with intermittent instillation of a local anesthetic agent may prove very useful in terminal cases with severe pain.

PELVIC CAVITY

Pain caused by malignant tumors in the pelvic cavity not only is difficult to manage but is frequently a frustrating problem even when blocks are used. The reason for this is that most malignant growths arising in the pelvic region develop from organs situated in the midline—for example the bladder, the prostate, the uterus and the rectosigmoid. This implies a bilateral innervation. Thus pain emanating from these organs is referable to both sides. An associated difficulty is the close relationship of the nerve supply of the organs in the pelvic cavity with the nerve supply to both lower extremities. In the lumbar area, such association is not so serious as to involve motor function extensively. In the sacral area however blocks

show a rise after the block provided severe arterio sclerosis is not present in which case there may be no change in temperature and pain may develop in the extremity. As with a splanchnic or celiac plexus block the complications that may develop are sub arachnoid injection, puncture of the vena cava or the aorta and penetration into the abdominal cavity with possible entry into a loop of bowel.

In terminal conditions where neurosurgical procedures may not be feasible an intrathecal alcohol injection may be performed. In these patients the disease has progressed to the point where it may be interfering with sphincter and lower extremity functions. Or radical surgery may have eliminated both bladder and rectal sphincter control so that the only complication that may be considered seriously is weakness of the extremity.

As an alternative a continuous peridural or caudal drip may aid temporarily in relieving the pain, but its effectiveness is limited in that either the catheter placed in the epidural space becomes plugged by granulation tissue or the patient develops resistance to the local anesthetic agent.

LOWER EXTREMITIES

The lumbosacral plexus which furnishes the chief nerve supply to the lower extremities lies in close proximity to the deep pelvic organs. Consequently malignant tumors of these organs are highly prone to affect this plexus. One of the common causes of pain

through the back and the actual procedure is similar to that of a splanchnic or celiac plexus block. The chief bony landmarks are the lumbar spines, the transverse processes, the 12th ribs and the iliac crests. The last two are helpful in locating the position of any of the lumbar spines.

Intradermal wheals are raised over the transverse processes of the lumbar vertebrae at a point 3-4 cm from the midline. The needle point is made to contact the transverse process and then partly withdrawn and redirected in a cephalad and medial direction so that it slides over the transverse process. The needle forms an angle of 30-45 degrees with the median sagittal plane, and it should establish contact with the body of the vertebra. An attempt should then be made to coax the needle to slide off the body of the vertebra. Ten cc of local anesthetic may be injected for each ganglion. This block may work effectively for uterus and perhaps bladder pain. For pain emanating from the areas of the rectum, cervix and prostate the sacral nerves may have to be blocked, in which case the sciatic nerves may be interfered with. If a lumbar sympathetic block is effective, 6 per cent phenol should be employed to produce a more permanent type of block. X-ray study with Diodrast is valuable for establishing precision in needle placement (Fig 10). An effective lumbar sympathetic block is indicated by a sensation of warmth in the corresponding lower extremity and of course relief of pain if the pain pathway courses through the sympathetic ganglia. Temperatures of designated spots on the leg will

for the incidence of post alcoholic neuritis is so high that it is doubtful whether absolute alcohol should be used at all for these peripheral nerves

A 29 year old man was referred to the anesthesiologist by the orthopedic and the neurosurgical clinics because of a persistent pain in the sole of the left foot following the excision of a painful neuroma. Infiltration of trigger areas in the scar proved unsuccessful because of the denseness of the scar tissue. A medial plantar nerve block was next attempted. Apparently this provided excellent relief of pain. The possibility of employing absolute alcohol was contemplated but was discarded temporarily in view of the proximity of the posterior tibial artery and vein. A lumbar sympathetic nerve block was next performed in order to determine how much of the pain was mediated through sympathetic pathways; there was none. A program of weekly blocks of the medial plantar nerve with a local anesthetic was instituted. Relief was very good and the intensity of the pain diminished considerably. The possibility of injecting alcohol was again contemplated since it was feared that too frequent injections into the medial plantar nerve would eventually be traumatic and cause neuritis. Therefore on introduction of the block needle during one procedure a direct contact with the nerve was obtained. Pain was relieved with 1 cc of local anesthetic. The needle was left in place and after 10 minutes 2 cc of absolute alcohol was instilled. Pain relief was immediate and persisted for three days after which severe post alcoholic neuritis developed. This was controlled by repeated blocks employing a long acting local anesthetic.

This case is a good illustration of the value of frequent repeated local anesthetic blocks and makes one question the sagacity of employing absolute alcohol for peripheral nerve blocks.

in the lower extremity therefore is involvement of the lumbosacral plexus by tumors arising from the uterus and its cervix the bladder the prostate and the rectosigmoid or tumors arising from the bony walls of the true pelvis Involvement may be in the form of pressure on the plexus or contiguous metastases Pain is usually referred all the way down to the foot Not only pain but often weakness of the lower extremities develops Pain may also be caused by the tumor pressing on the blood vessels to the leg thus interfering with its blood supply For this type of pain which develops secondary to pelvic conditions there is frequently an associated deep pelvic and sacral area of pain As was previously stated the nerve supply to the pelvic organs and the lower extremities are so intimately related that blocks applied to these nervous structures relieve pain in both the pelvis and the lower extremities Thus a lumbar sympathetic block such as an intrathecal alcohol injection to eliminate pain caused by masses in the pelvic cavity may also eliminate pain in the lower extremities

Pain may arise primarily from the lower extremity Tumors of bone may develop and cause severe pain and neuromas may give rise to pain What is more excision of a tumor or an extremity may leave a painful area or a phantom limb pain If the pain is localized in the foot or in the distal portions of the leg peripheral nerve blocks may work very effectively There should be a minimal loss of motor function with excellent pain relief However one may question the wisdom of instilling absolute alcohol into these nerves

diminish the convulsive seizures without excessive depression. The excitement evoked by the situation might provoke the administration of a larger dose than necessary and give rise to a temporary state of barbiturate poisoning and its consequent respiratory and central nervous system depression. Oxygen should be administered immediately and if the patient is apneic artificial respiration instituted. If there is hypotension intravenous administration of fluids should be started and vasopressors employed (desoxyepinephrine, Neo synephrine or norepinephrine). Norepinephrine should be used only under extreme conditions when the patient does not respond to the other vasopressors.

It must be emphasized that means for resuscitating the patient should be at hand whenever nerve blocks are to be performed. A simple anesthesia bag and face mask attached to a controllable source of oxygen is sufficient for the administration of artificial respiration. Intravenous fluids, vasopressors and an ultra short acting barbiturate should be available for immediate injection.

SUMMARY

Nerve blocks are not the final answer to the management of pain in malignancy. They constitute only one of the many methods that may be used to make the pain less acute. One should always be aware of their limitations but their value may be immeasurable when used judiciously in conjunction with other methods of treating pain.

PREMEDICATION

The use of the ordinary premedicants like morphine and scopolamine in patients suffering from pain due to malignancy might appear superfluous. These patients are often under such heavy doses of narcotics that further opiate administration is not necessary. The short acting barbiturates are probably more effective. Phenothiazine derivatives like chlorpromazine or phenergan when administered intravenously produce a tranquil sleeplike state from which the patient is easily aroused. What is most impressive in the use of these drugs is that the patient becomes quite cooperative. It is always better to have a conscious patient when a block is being performed for by paying close attention to the patient's symptoms and the sensations that he feels as the needle is being placed the physician may be warned and able to prevent complications.

REACTIONS TO LOCAL ANESTHETICS

Drug reactions may develop in a small percentage of cases. True reactions may excite the central nervous system and cause convulsions, or depress it and produce unconsciousness. Respiratory depression may also occur. The reaction may include the cardiovascular system and cause a marked hypotension. What is important however is that the developing reaction be recognized immediately and therapy instituted. If convulsions occur an ultra short acting or a short acting barbiturate should be administered intravenously to

nant disease Occasionally however following amputation for malignant disease, there is return of pain in the arm or leg without painful metastases elsewhere In such a case, a painful neuroma may be the cause of the patient's distress A single attack on the remaining portion of the nerve is usually warranted—single because in most instances it will not suffice nor will repeated attacks for a neuroma Injection of alcohol or formaldehyde into the nerve does not prevent the neuronal regeneration to which the pain is attributed If the patient is in a terminal state, regeneration may not occur soon and hence a single resection of the neuroma (with insertion of a polyethylene tube over the end of the nerve or incasement of the nerve in a tunnel drilled in the bone) is warranted If there are no other signs of metastasis and the pain recurs posterior root section may be attempted

When there are already metastases from a malignant disease of an extremity making amputation of the painful limb appear unwarranted peripheral nerve section is not indicated because overlap of sensory distributions would make section of numerous nerves necessary with considerable motor deficit as well as sensory loss Instead spinothalamic tractotomy would probably be indicated (see p 97)

CRANIAL NERVE SECTION

When pain arises from carcinoma in the distribution of the cranial sensory nerves peripheral section may

CHAPTER 3

Neurosurgical Aspects of Pain Management

NEUROSURGICAL TECHNIQUES for the relief of pain vary from peripheral nerve section to destructive procedures on the brain. Each has some drawbacks aside from the necessity of an operation, but the help and relief of pain can be so great that consideration should be given to such procedures. In order that the operation not be rendered unduly hazardous, neurosurgical attack should be considered before debility and addiction are advanced. The techniques described in the following pages range from the simplest attack on the peripheral nervous system to the most complex procedures on the central nervous system.

PERIPHERAL NERVE SECTION

There is little use for nerve section in the extremities as an independent procedure; the nerves may be cut in the course of amputation for sarcoma of the bone but not for most terminal or inoperable malignancies.

more common to use nerve root section or section of the descending pain pathways in the medulla oblongata

NERVE ROOT SECTION

By attacking the peripheral and cranial nerves near their origins or attachments to the brain and spinal cord it is possible to produce sensory loss without motor involvement

Posterior (dorsal) root section for the *peripheral nerve* elements entails laminectomy for any area below the head. A midline incision is made over the required number of spinous processes (One should remember that any one peripheral skin area is supplied by at least three and sometimes more posterior roots). The muscles and ligaments are detached from the spinous processes and laminae and the bony arches removed to allow access to the spinal dura mater. This is incised longitudinally and the dorsal roots isolated and cut. It is necessary to spare any large vessels on these roots especially on the 3d and 4th cervical the 4th and 7th thoracic and the 1st lumbar roots for these large radicular vessels may be the chief source of supply for the spinal cord especially in the thoracic area. If these radicular vessels are occluded softening of the adjacent spinal cord may result. The dura mater is then closed before suturing the muscles and skin. The operation is done with the patient prone (sometimes sitting for cervical root section) and it can be performed under local anesthesia although general anesthesia is usually more comfortable for a patient.

be undertaken but the possibility of regeneration in three to four months must be weighed against the probable survival time. The forehead and anterior scalp are supplied by the ophthalmic division (supra orbital branch) of the trigeminal nerve. This nerve can be avulsed readily under local anesthesia through an incision just above or just below the eyebrow. The resulting area of anesthesia can be extended by similar section of scalp nerves from the upper cervical roots and plexus (greater and lesser auricular nerves greater and lesser occipital nerves). Lesions of the side of the nose upper cheek and lip can be denervated by avulsion of the infraorbital nerve (branch of the maxillary division of the trigeminal nerve). Incision is made under local anesthesia in the mucosa over the first bicuspid area and the nerve grasped as it leaves the infraorbital canal. Sensation in the lower jaw (except for the lateral aspect of the skin overlying the middle of the ramus which is innervated by the upper cervical roots) can be abolished by section of the mandibular nerve as it enters the notch. An incision is made in a skin crease over the mandibular ramus and a small burr hole made through the bone over the mandibular canal. The lower teeth gums and chin can thus be anesthetized.

No other sensory cranial nerve can be readily approached for section. As a matter of practice it is relatively rare that trigeminal nerve branch section is done for pain in the face, for the local approaches cited above are almost always debarred by the local cancer for which relief is required. It is hence much

and nearby zones can be stopped by section of the trigeminal root in operation which has become standardized in the treatment of trigeminal neuralgia. Root section has the advantage that regeneration does not occur (as with peripheral nerve section) and the operation is done in a region usually remote from the carcinoma.

Under local or general anesthesia with the patient seated a vertical incision is made in front of the ear just above the zygoma. After separating the fibers of the temporal muscle a burr hole is made in the thin temporal bone and enlarged to a diameter of 5 cm (2 in.). The temporal dura mater is lifted from the base of the skull allowing access to the middle meningeal artery which is ligated, coagulated or compressed and cut. Medial and slightly forward the mandibular division of the trigeminal nerve is found. The dura mater is opened behind this division and the sensory root of the trigeminal nerve cut or avulsed. The temporal muscle and skin are closed in layers. Ordinarily patients in the sixties and seventies who have this operation for tic douloureux can be up in a day or two even though they are usually debilitated and the same is true of carcinoma patients. The death rate is less than 1 per cent. Facial paralysis or weakness attributed to stretching of a branch of this nerve is quite rare (less than 2 per cent) and permanent paralysis is almost unheard of. The motor branch of the trigeminal nerve is sometimes cut producing paralysis of the muscles of mastication on the same side but this rarely causes any distress in chewing or talk.

with intractable pain. The surgical trauma is dependent on the extent of the desired denervation, certainly enough exposure for section of the roots of three spinal nerves can be obtained without loss of so much blood as to require transfusion. The mortality should be no more than that of laminectomy for disk protrusion (less than $\frac{1}{2}$ per cent), and when the patient recovers from the anesthesia there should be no difficulty with bowels or bladder unless sacral roots have been cut. Convalescence takes from 7 to 10 days depending on the general condition of the patient. There is no motor loss from such a procedure and the loss of sensation is for all modalities.

Unfortunately such an operation is of limited usefulness for most visceral pain cannot be eliminated by posterior root section unless very extensive. However, just as angina pectoris may be overcome by section of the upper four or five thoracic roots pain of malignant disease of the chest with parietal pleural invasion can be similarly eliminated. Carcinoma involving the upper cervical plexus can also be handled in this manner. However section of the posterior roots contributing to the brachial plexus may not alleviate pain for reasons which are not clear and even if the pain is alleviated the limb is useless for without sensation effective motor function is impossible. However, when there has been amputation for malignant disease posterior rhizotomy may be very effective.

On the other hand *cranial sensory root* section is one of the most useful operations for the relief of intractable pain. Such distress anywhere in the face

closed. In most instances the patient can be up in a day or two, with very little headache. Sometimes ataxia of the ipsilateral limbs can result from retraction of the cerebellum but this is transient. Rarely there may be vertigo for a week or two from disturbance of the equilibratory mechanism. Mortality ranges up to 5 per cent depending on the status of the patient (usually poor with malignancy of the throat). In itself glossopharyngeal nerve section causes no detectable motor weakness in swallowing and the anesthesia of half of the pharynx is rarely disturbing to the patient. During the operation there is usually a transient elevation of blood pressure from section of the nerve roots (carrying the impulses from the carotid sinus) but this rarely outlasts the operation and even then lasts not more than a day or two. Bilateral glossopharyngeal root section can be carried out at the same sitting without much added risk—and again swallowing is not impeded. Indeed patients unable to swallow because of pain before surgery may be able to do so postoperatively.

In a very rare case pain in the ear due to cancer may not be relieved by glossopharyngeal upper vagal or trigeminal root section. The nervus intermedius, a sensory branch of the 7th nerve, may be involved. This nerve runs as a separate filament on the facial nerve and is usually hidden by the 8th. It can be cut by an approach similar to that for the 9th nerve (or posterior approach to the 5th nerve root) but if it is suspected that pain may be due to this nerve the operation should be done under local anesthesia or

ing Anesthesia of the cornea causes some concern especially if facial paralysis is already present (for example with parotid gland tumor) Suture of the lids to narrow the palpebral fissure may be carried out and certainly an eye shield should be used with careful and frequent inspection of the eye to insure absence of any foreign body It is sometimes possible to cut only the lower two thirds of the fibers of the root to preserve innervation of the eye and forehead if these parts are not involved in the pain

Relief of pain in the throat (and sometimes the middle ear) can be accomplished by section of the glossopharyngeal root (9th cranial nerve) This root is approached by a vertical incision medial to the mastoid bone usually under general anesthesia and with the patient lying in a face rest in the horizontal position Local anesthesia can be used if desired The nerve roots from the 7th to the 9th nerves are exposed by removing the bone medial to the mastoid process opening the dura mater and retracting the cerebellum to the opposite side The facial and auditory nerves (and often a separate nervus intermedius) can be seen entering the internal auditory meatus The 9th nerve arises by a series of rootlets from the lateral aspect of the medulla oblongata and these are cut separately It is common practice to include the first one or two rootlets of the vagus nerve as well for these may carry some sensation from the pharynx Extensive vagus section is to be avoided lest paralysis of the vocal cords and difficulty in swallowing arise Following root section the nuchal muscles and skin are

anesthesia, the cut can be made deeper or more dorsal as the case may indicate. The dura mater is then closed followed by layer closure of muscles, fascia and skin. Because of the interscapular location of the incision motion of the patient's arms is usually restricted for 5-10 days. If the section is made at the 2d thoracic level such restriction may not be needed. At the end of this time the patient can be allowed up.

The immediate loss of pain perception usually drops a segment or two in the first few days or weeks after operation. For this reason some neurosurgeons prefer to do the operation under general anesthesia and make a maximum cut immediately. The complications include death (usually less than 1 per cent at this operative site), temporary weakness or paralysis of the ipsilateral lower extremity (5-10 per cent) and loss of control of the sphincters. Urinary control may be interfered with in up to 5 per cent of the patients, bowel control in fewer patients. Touch and position sense are left undisturbed. Often the relief of pain is so sufficient that the patient begins to complain of pain on the opposite side present but of minor degree before operation (as in inoperable carcinoma of the uterus or rectum). It is then possible and proper to reopen the incision and make a similar cut on the intact side for relief of the residual pain. When there is midline or bilateral pain both cuts can be made at the same operation but they are then made at least one segment apart on the opposing sides so as not to impair the circulation of the spinal cord. When ever possible a weeks interval between the two cuts

with such anesthesia that the patient can be awakened at the time of nerve section, to allow mild electrical stimulation of the nerve. If such stimulation reproduces the pain then the nerve can be sectioned.

SPINOTHALAMIC CHORDOTOMY

Perhaps the most useful operation for relief of pain below the shoulder girdle is section of the pain pathways in the spinothalamic tract which runs in the anterolateral portion of the spinal cord. When this tract is cut in the upper thoracic region there is usually good somatic and visceral analgesia from the lower thoracic region caudally on the side opposite to the cut.

Under local or general anesthesia with the patient prone laminectomy is done at the 2d or 3d thoracic vertebral level. Usually the entire neural arch of one or two vertebrae is removed although there is a recent trend toward hemilaminectomy. The dura mater is opened to allow access to the dentate ligaments which hold the spinal cord to the interior of the dura mater. A pair of ligaments is cut, one is grasped and the cord is rotated. Then a sharp blade is inserted at the attachment of the dentate ligament to the cord and virtually the entire anterolateral quadrant of the cord is cut. If the patient's condition warrants the operation can be done under local anesthesia or under a short lasting general anesthetic so that the patient can be awakened for testing of the level of sensory loss after the incision is made. If there is insufficient

one to two segments) Cervical chordotomy can be accompanied by section of the upper three or four posterior roots on each side, to extend the level of anesthesia and also to help make the convalescence almost painless (since the incision is thus denervated) There is no impairment of healing by such sensory section Bilateral cervical chordotomies may be done often cervical chordotomy on one side may be accompanied by or followed by thoracic section on the other after a week or two This is believed to minimize sphincter and motor weakness With bilateral chordotomies there may be a frightening drop in blood pressure for some days after operation but this is transient and can be combated in the postoperative period by pressor drugs such as methamphetamine, still later, an abdominal binder and leg wrappings can be used as temporary measures while the patient adjusts to the vasomotor instability so like that of bilateral thoracolumbar sympathectomies

SPINOTHALAMIC TRACTOTOMY

The spinothalamic tract can also be cut anywhere from the spinal cord to the thalamus In the lower portion of the medulla oblongata the pain pathways lie laterally placed and can be cut by an incision in the lateral aspect of the medulla The pyramidal tracts are placed ventrally and there is little danger of injury to them The difficulties come from the pial vessels on the surface of the medulla and from the nearby descending root of the trigeminal nerve How

is best for this lowers the weakness which follows operation from 10 to 5 per cent and reduces the bladder complications of bilateral one stage procedures by half. Permanent sphincter paralysis may result and necessitate an indwelling catheter, with the risk of infection. This is not an important factor if the bladder and ureters have already been involved in the malignant disease process.

Failure to obtain relief of pain from a well planned unilateral operation may be overcome by cutting the second side in rare instances. Lack of success is attributed to failure of crossing of the secondary pain pathways in the spinal cord—an anomaly which can not be anticipated and which must be quite uncommon.

Spinothalamic chordotomy is also used to give relief of pain in cervical and upper thoracic segments (for example for pain in the upper extremity as with superior pulmonary sulcus tumor). The cut is then made at the 1st or 2d cervical level in a procedure which differs from the thoracic procedure only in minutiae. The exposure is more time consuming and somewhat more hazardous (3-5 per cent mortality) and there is less assurance of success, for the sensory level may drop in spite of what appears to be an adequate section. Nevertheless it can be very useful and is sometimes preferred to thoracic section even for abdominal pain. By using the higher level any unusual anatomic peculiarity may be thwarted (for example crossing of sensory fibers five to six segments above entry into the spinal cord instead of the usual

caudal to the inferior angle of the 4th ventricle (obex) and 6 mm lateral to the midline going as deep as 4 mm. Cerebellar ataxia is rarely a problem with such a caudal section. Pain and temperature sense are lost on the face (and often in the throat and ear as well). Touch is preserved so the dangers of corneal damage are greatly minimized. There is no interference with the muscles of mastication which may occur with posterior trigeminal root section.

The spinothalamic tract then burrows into the depths of the medulla and pons. Pontine attack by electrocoagulation has been attempted but is not actively used at present. The tract comes close to the surface again in the mesencephalon here it forms part of the lateral lemniscus along with secondary trigeminal and other facial sensory pathways. The operation involves making a large occipital flap elevation of the occipital lobe of the brain, section of the tentorium and visualization of the lateral aspect of the mesencephalon. A 5 mm incision is made across the brachium of the inferior colliculus ending at the inferior margin of the superior colliculus. Operative mortality reportedly ranges from zero to 80 per cent. The analgesia produced tends to fade and there has been considerable paresthesia in some patients. There is no disturbance of micturition and no risk of injury to corticospinal pathways. This operation should be considered an experimental one but it bears consideration in certain cases of carcinoma of the pharyngeal region where pain may be carried by the vagus nerve not amenable to nerve root section on both sides because

ever if this trigeminal root is partly cut the small zone of pain loss on the face will not prove to be very bothersome. The operation is more dangerous than cervical chordotomy (10-30 per cent mortality in different series) and is more difficult to carry out but it may give a very satisfactory loss of pain in the upper extremity and nearby neck.

Through a midline occipitocervical incision the occipital bone and first cervical lamina are exposed, the latter is removed and bone around the foramen magnum removed to allow opening the dura mater and access to the lower portion of the medulla oblongata. Just anterior to the line of emergence of the rootlets of the spinal accessory nerve a cut is made 6 mm deep and 4 mm dorsally. Testing of sensation can be carried out if the operation is done under local anesthesia. The lower portion of the dura mater is usually closed and the muscles and skin closed in layers. Some ataxia may follow the operation. The level of analgesia may drop with this procedure as with all tractotomies since some of the immediately postoperative sensory loss can be attributed to swelling and pressure on adjacent fibers. Bilateral medullary tractotomy has been fatal (presumably due to interference with vital centers in the bulb) and it is not done in one stage. If the neck is supported with a firm dressing the patient can be allowed up as soon as headache permits.

The same approach is used for section of the descending tract of the trigeminal nerve. This has a constant location and can be cut by an incision 6 mm

procedure is time consuming but thus far neither hazardous nor very painful. If all is well an electrolytic current is passed in to cause a small area of necrosis in the spinothalamic tract. The hazards of improper needle placement are obvious: the wrong locus may be damaged so that no anesthesia results or nearby structures may be damaged with unwanted effects. However, the accuracy of the lesion placement in the hands of the more experienced operators is sometimes astounding and such lesions may give relief of pain when nothing else can. How long the anesthesia will last and what paresthesias may result are questions that cannot be answered as yet. Obviously the same technic can be used to cause lesions in the end station for pain in the posterolateral nucleus of the thalamus. This is a large area and stereotaxic lesions may miss vital areas.

The radiations from the thalamus toward the cerebral cortex in the posterior limb of the internal capsule could also be attacked but the proximity of voluntary motor pathways and other sensory radiations have hindered such a procedure. Furthermore there is inadequate evidence that cortical ablations do not cause analgesia so it is unlikely that attack here is likely to arouse interest.

FRONTAL LEUKOTOMY

The use of destructive lesions of the frontal white matter for alleviation of pain arose as an incidental finding in patients with lobotomy done for mental illness. Actually there is no interference with primary

of the vocal cord and swallowing paralysis as well as respiratory complications

STEREOTAXIC LESIONS

The same locus in the mesencephalon can be reached by a needle inserted from the convexity of the skull and the tract destroyed by an electrocoagulation current. Accurate placement of such an electrode is dependent on a stereotactic instrument—a device for locating certain fixed landmarks in the brain and for placing the needle a designated distance from such a landmark. The wide range of head and brain size in man makes this task far more complex and difficult than in laboratory animals with less variable skull sizes (young adult monkeys, adult cats). There are a few centers in the United States and Europe where such instruments are in use, but in almost all centers patients are accepted only on an investigative basis. In brief, the procedures usually entail filling of the ventricular system of the brain with air and obtaining roentgen films of the ventricular system with a superimposed co-ordinate grid. A metal frame is affixed to the skull in a manner permitting exact reapplication at a future time. A drill hole is made through the skull in a location calculated to permit insertion of the needle to the desired site. Repeated co-ordinate and grid studies are carried out, usually basing the co-ordinates on a fixed neuroanatomic structure such as the pineal body or the posterior commissure nearby. A needle is inserted, brain waves are usually recorded and stimulation at the needle tip is carried out. The

pain with diminished psychological upset. In the few patients treated in this manner the results have been encouraging within the short follow up period.

A number of techniques have been used for lobotomy perhaps the safest is the following. Under local or general anesthesia the shaved scalp is infiltrated with procaine in line with the pupil of the eye. Incision is then made parallel to the long axis of the head (parasagittally) in the frontal region, to allow exposure of the coronal suture. A trephine opening is made just anterior to the suture line and the dura mater opened. Through a stab wound in the cortex a ventricular needle is inserted toward the posterior rim of the roof of the orbit. If the ventricle is encountered the needle is angled further anteriorly. With retractor and suction cautery the white matter of the frontal lobe is incised down to the gray matter of the orbital cortex medially and laterally to the corresponding cortical gray matter. A piece of Gelfoam containing air or a few drops of opaque oil is inserted to mark the plane of section in x ray films and the wound closed in layers after replacing the trephine bone button for cosmetic purposes. The contralateral side may be cut in a similar manner or only one side done.

It may be worth while to open the other side making sure to have a drill hole through the bone button and to coagulate the brain surface underneath before closing the wound. Thus the basic opening is ready for a future second stage procedure perhaps an open lobotomy or if desired a spinal needle can be inserted into the white matter (with x ray control).

pain pathways, the patient can still feel pain arising from within or superimposed from the outside. However, in the lobotomized patient the reaction to such pain is far different from the reaction in the normal person. Usually the patient makes no spontaneous complaint of pain and is not preoccupied with it. If pain does occur or is evoked the reaction is less intense and does not concern the patient. If narcotic addiction has been present dependency is relieved. Strangely enough after bifrontal leukotomy with drawal symptoms from abrupt cessation of morphine administration do not occur. The drawback to frontal leukotomy is the mental change produced in the patient; the predominant features are impaired judgment and deterioration in behavior. Incontinence, disorientation and apathy are commonly seen. Because of these symptoms unilateral leukotomy has been proposed to diminish the undesirable side effects. When effective the mental changes are much less marked. The decrease in spontaneous speech and the flattening or inappropriateness of emotional responses seen with unilateral operation are much less disturbing than with bilateral operation and pain and suffering may be reduced to a tolerable level. When the patient survives more than four to six months pain complaints are likely to recur after unilateral leukotomy. If suffering is again intense operation on the second side can always be carried out although at the price of severe psychological change especially in the early postoperative period. Section of only medial portions of the frontal white matter has also been aimed at relief of

MISCELLANEOUS PROCEDURES FOR RELIEF OF PAIN

INTRATHECAL ALCOHOL AND PHENOL

In patients with radicular and segmental pain corresponding analgesia may be obtained by injection of 95 per cent or absolute alcohol into the subarachnoid space. The technic is described in Chapter II, in brief spinal puncture is done at the level desired with the roots to be blocked uppermost. A small amount of alcohol is injected slowly and it rises to the dorsal roots. Heavy phenol solution can be similarly used with the painful side lowermost the chemical falls to the bottom of the subarachnoid space. These procedures are valuable in patients who are in too poor condition for chordotomy and have short life expectancy. Thoracic injections carry risk of transverse myelitis and lumbar injections may lead to weakness of the legs and sphincter incontinence.

SYMPATHECTOMY

There is little doubt that in some patients pain fibers run in the sympathetic chain and denervation by removal of these fibers may give relief of certain types of pain. Such visceral denervations are only temporarily effective in treatment of pain of malignant disease (for example splanchnicectomy for relief of carcinoma of the pancreas) for the tumor spreads to involve somatic nerves as well. Chordotomy is much

and procaine or alcohol can be injected to see what effect mechanical section of the frontal white matter can have on pain and suffering. Alternatively small burr holes can be made bilaterally and the dura mater and brain surface prepared for injections several days later. Graded injections can thereafter be carried out at leisure and the results of permanent white matter destruction approximated. These holes could also be used for graded destruction of the medial quadrants by electrolytic currents passed through needle electrodes (insulated except at their tips). For any of these "blind" procedures it is convenient to fill the ventricles with air or oxygen and to place the needles anterior to the ventricles as checked by x ray.

The operative mortality from frontal lobotomy should be less than 2 per cent. The danger of post-operative convulsions is about 10 per cent although such seizures are readily controlled by standard anti-convulsant medication.

In general frontal leukotomy should be reserved for pain which experience has shown does not respond to less radical procedures. The operation is considered strongly when the malignant process is a disfiguring one and is accompanied by much mental anguish. It is less demanding on the patient's resistance than say rhizotomy or chordotomy but ease of performing the operation should not blind one to the mental changes. Most neurosurgeons do not believe that lobotomy by transorbital route ("ice pick" operation) is of much value in intractable pain.

do not develop reoperation is advised. Complications are few and are principally those of the neurosurgical procedure (for instance blood clot) they can usually be handled quite effectively.

The contraindications to hypophysectomy for breast carcinoma include known metastases to the brain. Metastases here in the presence of a known source of active cancer are ordinarily not treated surgically since life expectancy is very short. On very rare occasions when headache, nausea and vomiting are exceedingly troublesome decompression by standard neurosurgical technics may be warranted. When the primary carcinoma has apparently been eradicated and signs of intracranial disorder appear operation should be considered. Long delayed metastases from hypernephroma and breast cancer are not unknown and if as is sometimes the case the metastasis is solitary operation may be lifesaving. Furthermore the intracranial lesion may not be related to the original cancer. The same considerations apply to tumors of the spinal cord for benign tumors of the spinal cord may become evident only after some carcinoma has been apparently removed. One should not believe that the spinal lesion is necessarily metastatic without making further investigation. Because spinal metastases are so rapidly productive of paraplegia—and this does not imply imminent death—most neurosurgeons believe in decompressive laminectomy even for known metastatic disease to the spine in the hope of delaying the immobility and nursing problems of paraplegia.

more effective in such cases. However, as a temporary measure for patients in poor physical condition, para vertebral injections of alcohol may damage the sympathetic chains enough to give considerable relief. The techniques are described in Chapter II.

HYPOPHYSECTOMY

There has been considerable success reported in alleviating pain of metastases and in improving the patient's condition generally from hypophysectomy for breast carcinoma but the operation appears to have little indication in other types of malignant disease in which trials have been made. There appears to be less postoperative distress to the patient than after adrenalectomy. To be effective, all of the hypophyseal anterior lobe must be removed.

A standard right frontal craniotomy approach can be used, with more room obtained by continuous spinal drainage during the procedure. The stalk of the hypophysis is clipped and cut, the diaphragma sellae incised and the gland evacuated by curettage. To help insure destruction of small residues of gland, Zenker's solution is instilled into the cavity. The mortality rate is 3-5 per cent but the postoperative course is usually smooth. No particular endocrine therapy need be given preoperatively but maintenance doses of cortisone are given after operation. Effectiveness of removal can usually be measured by quantitating the responses to cortisone. If the signs of hypophyseal inadequacy

on the sympathetic nervous system. In malignancy this is rarely effective unless the cancer is still restricted within the capsule of the viscus. When there has been spread, spinothalamic tractotomy should be employed. Unilateral section may be sufficient when the pain is unilateral.

THORAX

The pain of breast and lung carcinomas may be the most difficult to handle. It is frequently bilateral and involves the upper extremities. When the pain is unilateral and the upper extremity is weak, swollen and useless, posterior root section may be performed although a long laminectomy may be needed to denervate the arm completely. Otherwise chordotomy at the 1st cervical level or section of the spinothalamic tract in the medulla oblongata may give a satisfactory level of anesthesia. In cervical chordotomies, bilateral section of the posterior roots makes convalescence from the operation more pleasant without incapacitating the patient. Although bilateral cervical chordotomy can be done at one sitting, two stages are preferable. Unfortunately, the operation may not always give lasting relief from pain. In this event, unilateral frontal leukotomy or bilateral medial frontal quadrant section may be quite effective.

NECK

Pain restricted to the region between the ear and the clavicle (as in carcinoma of the submaxillary area)

NEUROSURGICAL ASPECTS OF PAIN BY REGION

PELVIS

Carcinomas in the pelvis may lead to pain in the low back, buttocks legs lower abdomen and pelvis. Anterolateral chordotomy is the treatment of choice especially when the pain is unilateral. The family should be aware of the frequent postoperative complaint of contralateral pain which probably exists before operation but is unmasked by the relief of the major pain. Second stage operation can be done through the same incision in five to eight days. Such staged bilateral operations are less likely to produce sphincter disturbance than simultaneous section of both tracts. The major complications are weakness paresthesias of the analgesic legs sphincter disturbance and temporary hypotension. When the carcinoma has led to colostomy and bladder drainage, and the pain is limited to the penis perineum and saddle area the patient may well be in too poor condition for surgery and in such a patient the injection of alcohol into the lumbosacral subarachnoid space may suffice to make the pain disappear. In rare instances there may be persisting pain often of a burning nature following any procedure for relief of pain even with good analgesia for external pain. When this occurs leukotomy of some sort is indicated.

UPPER ABDOMEN

Pain from nonmalignant disease of the pancreas liver stomach etc may often be relieved by attack

CHAPTER 4

Humoral and Chemical Palliation of Malignancy

IN MALIGNANCY the use of agents or procedures to alter the humoral balance has one primary objective—to produce an environment unfavorable to the growth and development of the neoplasm. In favorable circumstances a decrease in the size of the primary or secondary malignancy is temporarily possible. Unfortunately, although many hormones are available as pure chemicals and although complete surgical removal of an endocrine gland is possible, the effects are not simple. For example, the results of the administration of an estrogen are not confined to the production of a single phenomenon. The direct effects of any hormone are multiple and complex, and the magnitude and implications of these effects are compounded by the complexities and interrelationships of the entire endocrine system. The stability of the internal environment rests on a continually fluctuating and dynamic system of balances. If we upset this equilibrium by introducing a massive weight of one hormone or by

may be handled effectively by section of the first four or five cervical posterior roots. When the cervical pain is associated with arm or chest pain, spinothalamic tractotomy is added. When suffering is great and there is fear of strangulation or death from hemorrhage, leukotomy may be chosen as the first procedure.

FACE AND THROAT

Section of the trigeminal, glossopharyngeal and upper vagal nerve roots is usually adequate to relieve unilateral pain in the face and throat. Section of the trigeminal pathways in the medulla oblongata may be useful when combined nerve root sections are needed or when access to the middle fossa is prohibited by a malignant lesion in the vicinity. When there is considerable psychic disturbance, as with disfiguring lesions, leukotomy may be performed first. In such a case, spathy may be a desirable goal.

SUMMARY

Most neurosurgical procedures for relief of pain for terminal carcinoma require a major operation and cannot be done if the patient is in too poor condition. Because such operative relief of pain may be well worth while, consideration of such procedures should not be too long delayed. In general, operative relief of pain should be considered when the patient's pain is no longer relieved by codeine and when life expectancy is two months or more.

extremely ill patient hauled from town to town or spend his last few pennies or those of his relatives attempting to find the panacea. Some of these alleged "cures" are promoted by well intentioned individuals with inadequate knowledge of the natural course of the disease, but all too frequently an utterly worthless agent receives unwarranted acceptance merely because it is sponsored by someone who has achieved fame in other fields. Fortunately the National Research Council has established a Committee on Cancer Diagnosis and Therapy, which is willing to screen any "cancer cure" and at the same time protects the interests of the inventor. The drugs are distributed to expert and experienced investigators who report their clinical and scientific observations to this Committee. A physician can obtain information on any of these so called cures from the National Research Council Committee on Cancer Diagnosis and Therapy, 2101 Constitution Avenue, Washington 25, D.C.

The discussion of procedures and therapy in this chapter is limited to those situations where there is no possibility that the malignancy can be eradicated by surgery or radiation. Therapy with hormones or chemicals must however be considered in relation to the other techniques available for the management of malignancy. It is our purpose to outline the role of the internist as a member of a team all of whom are contributing toward the alleviation of the pain and suffering associated with cancer. The discussion is divided into two general sections: (a) a description of the clinical management of the more common types

cutting off the source of another the resulting imbalance produces widespread and varied effects on the host. Thus, we can never produce only the single desired effect by such technics we may partially achieve our goal but at the price of other derangements.

The introduction of specific chemical agents in the management of malignancy must be considered a calculated risk. The ideal agent is one which exerts the desired effect on the target cell or organ without producing any other pharmacologic effect. There is no chemotherapeutic agent which meets this requirement. At best we hope to depress a malignant condition in the host by substituting the lesser toxicity (we trust) of the chemotherapy. The foregoing should not be interpreted as negative or discouraging statements because therapy with hormones and chemical agents has demonstrated that a variety of tumors are not entirely autonomous in their growth and that they can be influenced profoundly albeit temporarily by these agents. When it is impossible to cut out or burn out a tumor chemotherapy provides a valuable third approach.

A physician caring for a patient with incurable metastatic cancer is frequently besieged by well meaning relatives and friends who suggest certain forms of therapy that have received great notoriety through the lay press advertisements or hearsay. It is the responsibility of the attending physician to make a decision as to whether it is worth while to try any of these agents. There is nothing much more tragic than having an

extremely ill patient hauled from town to town or spend his last few pennies or those of his relatives attempting to find the panacea. Some of these alleged "cures" are promoted by well intentioned individuals with inadequate knowledge of the natural course of the disease but all too frequently, an utterly worthless agent receives unwarranted acceptance merely because it is sponsored by someone who has achieved fame in other fields. Fortunately the National Research Council has established a Committee on Cancer Diagnosis and Therapy which is willing to screen any "cancer cure" and at the same time protects the interests of the inventor. The drugs are distributed to expert and experienced investigators who report their clinical and scientific observations to this Committee. A physician can obtain information on any of these so called "cures" from the National Research Council Committee on Cancer Diagnosis and Therapy 2101 Constitution Avenue, Washington 25 D C.

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of malignancy that may be influenced favorably by alterations in the humoral balance or by chemotherapy, and (b) brief descriptions of some of the more important pharmacologic characteristics of the agents used in therapy.

CLINICAL MANAGEMENT OF MALIGNANCY

CANCER OF THE FEMALE BREAST

Unfortunately one of the most common malignancies cancer of the breast is cured by definitive therapy in less than half the cases. Because of the nature of the spread of the disease into the viscera and bone great disability and pain ensue. Characteristically metastatic cancer of the breast is a slow killer but produces increasing suffering that may last for many months or years. Any procedure that temporarily rehabilitates such people seems justifiable. It is fortunate that many cancers of the breast do not show complete autonomy of growth and certain specific forms of therapy will temporarily alter the course of the disease markedly. Although these procedures are of only temporary benefit there is under the best of circumstances worth while rehabilitation of previously bedridden patients for as long as two or three years.

ESTROGEN THERAPY—Pharmacologic doses of estrogen cause tumor regression in about 50 per cent of patients when the primary tumor develops in a patient ten or more years postmenopausal. Dramatic regression of soft tissue metastases occurs in some patients. Osteolytic metastases may also show recalcification.

Although this is not demonstrable by roentgenography for several months. Along with tumor regression pain relief improvement in general health and control of other symptoms due to the localization of the metastases can be expected to occur.

On the other hand some patients may show an apparent augmentation of tumor growth during estrogen therapy. This is more common in the pre or immediately postmenopausal patient. It is therefore of the utmost importance that the patient be under very close observation for the first few weeks of therapy. However, rather acute swelling and increased pain in the soft tissue lesions during the first two weeks of therapy may precede a period of major regression of the tumor and so it is wise to continue therapy for at least one month before concluding that the estrogen is producing an augmentation. Regressions may continue under this therapy for from four months to several years. In general an estrogen produced regression is more complete and of longer duration than an androgen produced regression.

The mechanism by which estrogens produce temporary regression is not understood. It has been postulated that the common tumor of the breast in the postmenopausal woman consists mainly of cells that cannot grow in a substrate containing estrogens. However malignant cells that require estrogen for growth are present in small number. Thus administration of estrogen depresses the dominant cells and thereby the total tumor mass shrinks. In time however the tumor reappears in the same site and it is not affected by

of malignancy that may be influenced favorably by alterations in the humoral balance or by chemotherapy and (b) brief descriptions of some of the more important pharmacologic characteristics of the agents used in therapy

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The physiologic actions of estrogens must be borne in mind when administering large doses of the hormone. Withdrawal bleeding even in the aged patient is the rule. Regrowth of atrophic uterine fibroids may occur and reactivation of chronic cystic mastitis is common. We have observed hematomata in two aged patients with stenosis of the cervical os. Since interrupted therapy causes frequent episodes of uterine bleeding, it is advisable to give continuous therapy until bleeding occurs and then omit the drug until bleeding has stopped. (If bleeding does not stop in 10 days 100 mg progesterone intramuscularly may be given for 5 or 6 days.) Therapy should be continued until evidence of progression or augmentation develops or until all clinical evidence of metastatic disease has disappeared (a rare situation). Treatment may be reinstituted when the disease becomes reactivated and a second, third or fourth regression may occasionally be produced. Usually, however, the tumor becomes less and less responsive to the hormone.

Estrogens given to the aged patient for metastatic cancer of the breast not infrequently produce other benefits such as revitalization of the atrophic skin and mucous membranes and reappearance of subcutaneous fat, producing improved tissue turgor. On the other hand, estrogens in high doses produce sodium retention and congestive heart failure may develop unless proper cardiac management is instituted. Also, patients

continuing the estrogen therapy. This hypothesis is supported by the fact that it is not uncommon to observe a secondary tumor regression on cessation of estrogen therapy in an individual who has previously responded favorably and then relapsed while still receiving estrogen. Another possible explanation of the depressing effect of estrogen on cancer of the breast is that high doses of the hormone depress the hypothalamus which produces certain hormones favorable to tumor growth (somatotropin?, prolactin?).

Regression of metastatic cancer of the breast has been reported with doses of from 3 to 500 mg of diethylstilbestrol a day. It is probable that 15 mg daily will accomplish as much as larger doses and less than this amount may not be sufficient in most cases. The estrogen is given orally in three divided doses after meals. About 25 per cent of the patients complain of nausea during the first week of therapy but only rarely a patient unable to tolerate the drug. Antiemetic drugs may be of help in some cases. If the patient is unable to tolerate this dose of diethylstilbestrol by mouth she will probably experience the same discomfort with the equivalent dose of other estrogens given orally although ethinyl estradiol 1 mg or conjugated estrogenic substances (for instance Premarin) 30 mg may be substituted. If oral medication is not tolerated, the intramuscular administration of estradiol benzoate or dipropionate, 5 mg twice a week may be substituted. The long acting estrogens are less satisfactory because of troublesome prolonged uterine bleeding on omission and the added hazard

been doing the patient a favor by giving androgens because of the emotional impact produced by masculinization. On the other hand, the euphoria and increased libido seem to be welcomed by other patients. Before embarking on androgen therapy it is wise for the physician to size up his patient in order to predict the psychological reaction to masculinization. We have seen many patients who bitterly resented the results of androgen therapy.

Androgens are most conveniently given in the form of methyl testosterone 25 mg four times a day by mouth. Nausea sometimes occurs with this dose in which case 100 mg testosterone propionate in oil may be given three times a week intramuscularly. The long acting intramuscular preparations carry with them the same objections as the long acting estrogens and are even more hazardous because of the greater frequency of hypercalcemia during the use of androgens. The so called "weaker" androgens are not recommended since it is now apparent that the palliative effect depends on the androgenicity of the product. The tumor depressing effect of androgens is not understood; it may be due to neutralization of estrogens or to depression of the anterior hypophyseal hormones. Androgens should be continued for a minimum of two months before being discarded as a means of palliation unless psychological or clinical contraindications are apparent. The drug is highly anabolic, and most patients have an increased appetite, feel stronger and develop an improved hemogram or even polycythemia. Because of marked sodium retention re-

with extensive osteolytic metastases may develop dangerous hypercalcemia during estrogen therapy. The sudden development of nausea and lethargy should be considered as signs of hypercalcemia until disproved by normal serum calcium values or negative Sulkowitch reaction of the urine. Radiation has been used in conjunction with similar doses of estrogens in the younger age group by Dr. Ira Nathanson who felt that estrogens seemed to increase the effectiveness of radiation therapy.

ANDROGEN THERAPY—Androgens in large virilizing doses produce temporary regression in about 20 per cent of patients with metastatic cancer of the female breast. The regression of the soft tissues is usually not so definitive as with estrogens but is effective in the same proportion in all age groups. Recalcification of osteolytic metastases is demonstrable sooner than that produced by estrogens and pain from osseous lesions is more effectively relieved. It is of interest that pain relief occurs in about 65 per cent of the patients suffering with osteolytic metastases although recalcification of the lesions is demonstrable in only about 16 per cent. It is not uncommon for the patient to experience an increase in pain during the first two weeks of therapy and later obtain gratifying pain relief.

The major objection to the use of androgens are the disfiguring effects of masculinization together with distortion of the psyche. Even in patients receiving considerable pain relief and temporary tumor regression it is sometimes doubtful that the physician has

been doing the patient a favor by giving androgens because of the emotional impact produced by masculinization. On the other hand, the euphoria and increased libido seem to be welcomed by other patients. Before embarking on androgen therapy it is wise for the physician to size up his patient in order to predict the psychological reaction to masculinization. We have seen many patients who bitterly resented the results of androgen therapy.

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striction of this element is frequently necessary. For this reason it is usually unwise to use androgens in the presence of considerable ascites, pleural effusion, borderline congestive failure or severe lymph edema.

OOPHORECTOMY—Although oophorectomy was reported to be of value in far advanced cancer of the breast in the last part of the nineteenth century, it has not been used extensively as a means of palliation until recently. Radiation castration is fairly popular but it has the disadvantage of not completely arresting ovarian estrogen production in many cases. It is curious that a well documented series of cases of surgical castration for metastatic cancer of the breast in the female has not been published. Experience shows that surgical castration can produce temporary regression of this disease not infrequently in menstruant and those early in the menopause and it is usually superior to androgen therapy because of the greater chance of palliation and fewer side effects. Put to a vote most women would rather have hot flashes and dizzy spells than whiskers and a male voice. Therefore oophorectomy is indicated in the menstruant at the first sign of visceral or osseous metastatic disease. Following failure of this procedure androgens could be tried.

ADRENALECTOMY—On the hypothesis that extra ovarian estrogens are produced by the adrenal cortex and that many malignancies of the breast are estrogen dependent, bilateral total adrenalectomy after obliteration of the ovaries has been performed by several clinical groups. This has produced gratifying palliation

in 18-25 per cent of the patients. Palliation following this procedure has lasted from six months to three years. Because of the extensive surgery involved and the need for careful supervision of replacement therapy the rest of the patient's days, it would be gratifying if it were possible to select patients who would be sure to respond favorably. Huggins feels he can predict response by the cell cytology of the primary untreated tumor, the tumor showing a high degree of differentiation being the most likely to respond. Others have not been able to make such distinctions. All are agreed that the slow growing tumor is more likely to show a favorable response and that in the highly anaplastic tumor failure is usual.

The management of replacement therapy in adrenalectomized patients is as follows. Starting 24 hours preoperatively 50 mg cortisone is given intramuscularly every six hours. Just prior to surgery, 100 mg cortisone is administered orally and 1,000 ml normal saline solution is given intravenously. If evidence of shock develops during surgery hydrocortisone is administered intravenously and methoxamine (Vasoxyl) is used to maintain blood pressure. Five mg desoxycorticosterone may be given on the day of surgery and the first postoperative day although this is usually unnecessary. Following surgery cortisone is given in doses of 50 mg every four hours for four doses every six hours for four doses and then gradually reduced to 50-75 mg per day in divided doses according to the patient's requirement. Extra sodium chloride is added in doses of 3 Gm or more

daily depending on the estimated amount of electrolyte loss. The administration of potassium is practically never indicated and may precipitate acute adrenal insufficiency. The route of administration of cortisone and salt depends on the patient's tolerance to oral medication. Care must be taken to maintain fluid balance and blood must be replaced as indicated. Hydrocortisone should be added by slow intravenous drip if signs of adrenal insufficiency develop. Usually the maintenance dose of 50-75 mg cortisone may be instituted by the fourth or fifth postoperative day. Before discharge from the hospital the patient and her family must be briefed thoroughly as to management especially during any period of stress when the dose of cortisone must be increased manyfold temporarily. The combined procedures of castration and adrenalectomy are of questionable value in patients nearing the terminal stage of the disease. This procedure gives the greatest palliation if performed before irrevocable damage has occurred. It is important also not to select patients who are irresponsible.

HYPOPHYSECTOMY—Because of technical difficulties earlier attempts to perform total hypophysectomy for palliation of cancer of the breast resulted in permanent brain damage and incomplete removal of the organ. Recently the frontal approach has greatly reduced the morbidity and improved the completeness of hypophysectomy. It has been suggested that palliation following successful complete hypophysectomy is equal to castration adrenalectomy. The withdrawal of certain other pituitary hormones as well as cor

tiotropins and gonadotropins, may further suppress tumor growth. Replacement therapy following hypophysectomy is similar to that following adrenalectomy. A temporary or permanent diabetes insipidus may require the administration of vasopressin tannate in oil (Pitressin). Hypophysectomy is still in the experimental stage and should be limited to centers where a careful evaluation of the results can be made.

CANCER OF THE MALE BREAST

Surgical castration or high doses of estrogens produce tumor regression in about 60 per cent of men with metastatic cancer of the breast. Adrenalectomy and hypophysectomy have both been shown to produce regressions after the tumor escapes from the effect of the previous procedures. Surgical castration and the administration of estrogens in the male are discussed below.

CANCER OF THE PROSTATE

Because of the frequency of cancer of the prostate in elderly men and the fact that it is seldom recognized before it has extended beyond the possibility of surgical obliteration, this is the most common type of metastatic tumor seen by the family physician in the male. Like cancer of the female breast, this tumor metastasizes extensively, especially to the bone and viscera, and thereby produces many debilitating and painful lesions. Months or even years may elapse before death, during which the patient goes through

great suffering. Fortunately, however, this tumor is not entirely autonomous in its growth and responds to certain steroid manipulations as does cancer in the female and male breast. These procedures can provide great palliation for anywhere from three months to eight or nine years, during which time the patient may be rehabilitated and can carry on a relatively normal life, although at no time is the tumor so completely depressed that it disappears.

CASTRATION—Removal of the testes eradicates most of the circulatory androgens. In general, the growth of cancer of the prostate is stimulated by androgens and inhibited by their withdrawal. Castration can provide dramatic relief from crippling bone pain and pain due to tumor encroachment of sensory nerves or vital organs. Urinary retention may be corrected with definite shrinking of tumor tissue. Cough and dyspnea produced by invasion of the pleura and pulmonary parenchyma may be relieved dramatically. These results are due to a specific effect on the metastases as demonstrated by roentgenographic and cytologic evidence. A dramatic decrease of the elevated serum acid phosphatase is further evidence of the specificity of the reaction. About 65 per cent of all cancers of the prostate are favorably influenced by castration. Good palliation may last from three months to a number of years. The results, however, are temporary, since the tumor finally escapes from the effects of this androgen withdrawal. Estrogens are used in conjunction with castration with apparent beneficial effects; this may be due to the fact that some Leydig

cells are occasionally preserved especially when the tunica albuginea testis is left intact. It would appear that if a patient accepts a procedure such as castration the surgeon should take every means of removing all testicular sources of androgen production.

ESTROGENS—Chemical castration may be obtained by the use of estrogens in the male. Five mg diethylstilbestrol (or its equivalent) daily will provide similar but not as prompt relief as that obtained by surgical castration. Estrogens suppress pituitary gonadotropins thus producing atrophy of the testes. In some cases the combination of surgical castration and administration of estrogens seems to be of greater palliative value than either therapy alone. It is possible that the estrogens by depressing gonadotropin may suppress extra gonadal androgen formation.

ADRENALECTOMY—Since the adrenal cortex secretes androgenic steroids it is not surprising that when palliation eventually fails after suppression of gonadal sources of androgen removal of the adrenals will be of renewed aid in palliation. It also appears that, when neither castration nor estrogens have been of value adrenalectomy will also fail. This is probably due to the fact that some prostatic tumors are entirely autonomous. Palliation following adrenalectomy in patients in relapse after either chemical (estrogen) or surgical castration is usually of short duration. Because of this some clinics have dropped this form of therapy. However, adrenalectomy produced palliation has been known to last as long as 2½ years. The management

of adrenalectomized patients has already been described

HYPOPHYSCTOMY—Recent improvements in the technic of hypophysectomy have provided a means of depressing prostatic tumors through the suppression of both cortical and gonadal testosterone by removing gonadotropin and corticotropin production. There is some evidence that the pituitary growth hormone may also influence tumor growth; therefore hypophysectomy may have the advantage of producing in a single procedure greater palliation than that provided by castration and adrenalectomy. Earlier attempts to obliterate the hypophysis by radiation were unsuccessful because the amount of radiation required injured the adjacent brain tissue. Recently, the hypophysis has been destroyed by the use of radioactive yttrium placed directly into the hypophysis.

ADRENAL CORTICOMDS—On the theory that corticoids in high doses can produce atrophy of the adrenals, 200 mg cortisone (or its equivalent) daily has been used in prostatic cancer. Marked pain relief, especially that of bone pain, can be obtained by this technic, but evidence of suppression of adrenal androgens is lacking. It is more likely that this palliation is due to the anti-inflammatory effects of the corticoids rather than to any specific repression of the tumor.

ANDROGENS—Occasionally patients in relapse after orchidectomy will show general improvement when androgens are administered. There may be improved appetite, increased strength and a sense of well-being. However, no tumor regression occurs and the sub

jective improvement is probably due entirely to the expected effect of replacement therapy in a castrate. More often androgens will produce increased pain and debilitation in these patients.

USE OF HORMONES IN OTHER SOLID TUMORS

Both testosterone and estrogens have been tried in various other types of tumors with negative results although because of the anabolic action of testosterone weight gain increased strength and improved hemogram may occur. Preliminary reports suggested that progesterone might be of value in cancer of the cervix but more complete studies have shown this to be without effect. Estrogens may by their action on the mucous membrane of the vulva decrease the necrosis and promote some healing in far advanced cancer of the cervix but they have no inhibiting effect on the growth of the tumor. The effect of cortisone and corticotropin in lymphomas and leukemias is discussed below. These drugs have a valuable place in the nonspecific palliation of far advanced malignant disease in general. Control of fever, reduction of inflammatory reactions, relief of pain, improved appetite and general feeling of relief may be obtained temporarily in many patients. Corticoids and corticotropin are not used often enough in far advanced malignancies probably because the action is nonspecific and does not affect the growth of the tumor itself. If the patient is made to feel better this is a real contribution. These drugs are of especial value in pulmonary

malignancy, whether primary or secondary, by improving the airway and decreasing edema and secretions. Corticoids in large doses may produce temporary regression in cancer of the breast and have been shown to control hypercalcemia at times.

MALIGNANCIES OF THE RETICULOENDOTHELIAL SYSTEM

HODGKIN'S DISEASE—The course of Hodgkin's disease can be altered by three general approaches: radiation, chemotherapy, and steroid therapy. Radiation and most of the chemical agents act by virtue of their cytotoxic properties. Mitosis is inhibited or arrested, and there is evidence of changes in the structure and functions of the chromosomes. These effects are more pronounced on rapidly proliferating cells. Although all germinal tissue is susceptible from a clinical standpoint, the most important effects on normal tissue are observed in the bone marrow and lymphoid structures, with less significant effects on the intestinal mucosa, gonads, and cornea. Nitrogen mustard, TEM, and TEPA are all effective in producing temporary regressions in Hodgkin's disease similar to those provided by radiation. Chemotherapy may be given previous to, in conjunction with, or following radiation therapy, depending on individual circumstances. However, careful hematologic studies must be made in order to prevent too great a depression of bone marrow function. Radiation is generally the treatment of choice when the disease is localized and chemo-

therapy is usually used first if the disease is generalized. The response to chemotherapy (relief of pain, pyrexia, pruritis, etc.) may be observed in a few days. If chemotherapy does not prove effective, it can be abandoned temporarily in favor of radiation, following which it may be reinstituted to good effect. In those patients who develop anorexia, generalized weakness, etc., corticotropin, cortisone, or certain other corticoids may provide valuable additive therapy. Corticotropin and corticoids produce shrinking of the tumor, stimulation of the bone marrow, and relief of pruritus, pain, and hyperpyrexia. Used in conjunction with radiation or chemotherapy, they frequently depress the unpleasant side effects of these procedures.

LYMPHOSARCOMA.—Nitrogen mustard, TEM, corticotropin, and cortisone have proved to be of value in the palliation of lymphosarcoma. The folic acid antagonists are occasionally effective, but their use should be reserved for those cases which fail to respond to other forms of therapy. Radiation is an important and useful technic in the management of lymphosarcoma. Corticotropin and cortisone can be used in conjunction with nitrogen mustard or TEM, or alone, in the same manner as described above in Hodgkin's disease, with gratifying but temporary results. Corticotropin and the corticoids can be particularly useful when the patient has become refractory to other forms of therapy. Reticulum cell lymphosarcoma occasionally responds to treatment with nitrogen mustard or TEM. Partial remissions are usually obtained in case of lymphocytic lymphosarcoma, and

the best results are most often seen in cases of giant follicular lymphosarcoma using both nitrogen mustard or TEM and corticotropin or cortisone

CHRONIC MYELOCYTIC LEUKEMIA.—Myleran (1,4-dimethanesulfonylbutane) may prove to be the drug of choice in the treatment of chronic myelocytic leukemia. Radiation is usually more effective than nitrogen mustard. TEM, urethane and 6-mercaptopurine (Purinethol). ThioTEPA (triethylene thiophosphoramide) is being used experimentally, and colchicine (and its derivatives) has been employed in this disease although the latter drug does not significantly alter the course of the leukemic process. Fowler's solution may be used advantageously in the early course of the disease; however it must be noted that every accepted form of therapy shows to advantage in early myelocytic leukemia.

CHRONIC LYMPHOCYTIC LEUKEMIA.—This disease must not be treated on the basis of elevation of the white count only. If the count is 100,000 and no anemia is present, and if no symptoms referable to the disease cause discomfort, then no therapy is indicated. Since this disease is favorably influenced only temporarily by radiation, chemotherapy (nitrogen mustard, TEM, TEPA, ThioTEPA) and corticotropin or corticoids, these agents should be used only when necessary for the welfare or comfort of the patient. The rule here is "Don't treat the blood count—treat the patient."

ACUTE LEUKEMIA.—The prognosis in acute leukemia is discouraging. However, if we consider that it is now possible to prolong life by months or a year or

more we have reason for hope that we are on the right track and that eventually more rewarding results may be obtained. If with modern therapy we can make the terminal months of a child's life comfortable and free of misery, this is of no little consideration to the patient, the family and the physician. Nitrogen mustard, TEM, Myleran and urethane are of little or no value. Fortunately there are three groups of agents of proved merit: corticotropin and the corticoids, folic acid antagonists and 6-mercaptopurine. Although resistance to these drugs always develops, it is clinically important that there is no cross transfer of resistance. This makes it possible, for example, to achieve an effective result with 6-mercaptopurine after resistance has developed to the folic acid antagonists. The effects of corticotropin or corticoids are usually seen soon after institution of treatment, whereas 6-mercaptopurine and the folic acid antagonists require three to four weeks before their effects are significant. Accordingly corticotropin or corticoids is the treatment of choice in the acutely ill patient either at the onset of the disease or during an exacerbation while under treatment with other agents. Courses of therapy with any of these three groups of agents may be given sequentially or concurrently depending upon the clinical condition of the patient. It should be noted that the folic acid antagonists are usually ineffective in acute monocytic leukemia. Also all of these agents appear to be more effective in children than in adults. Acute leukemia in adults may respond to the combination of 6-mercaptopurine and corticotropin or corticoids. The

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lymphoblastomas particularly in the early stages of the disease when the lesions are minimal in size. Nitrogen mustard and TEM are generally most useful. Corticotropin and corticoids will temporarily relieve pruritus and promote healing of the lesions.

PHARMACOLOGIC PROPERTIES OF HORMONES AND DRUGS

CORTICOTROPIN AND CORTICOIDS

CORTICOTROPIN (ACTH adrenocorticotrophic hormone) is available as aqueous and gel solutions in standard and high potency form but the most convenient form is the high potency gel because of the ease of administration and the need for only one injection a day or every two days in comparison to the necessity of giving the aqueous solution every four hours for maximum effect. For more rapid effect it can be used in 10 per cent dextrose by slow intravenous drip over a 12 hour period. For maximum cortical stimulation 80-100 units of corticotropin gel (40 units per cc) is given once daily for two or three days and gradually reduced to a maintenance dose of 20-40 units a day depending on the condition treated. Because the drug is given daily the patient is usually instructed in the insulin technic using a U40 syringe.

Corticotropin is useful in acute leukemia, the lymphomas, chronic lymphatic leukemia and multiple myeloma and is also of value with radio or chemotherapy in blocking some of the myeloid depressing effects and radiation sickness. At times it gives good

use of very large initial doses of prednisone may prove to be the treatment of choice. According to some investigators corticotropin and cortisone are contraindicated in acute myeloblastic and monocytic leukemia.

MULTIPLE MYELOMA—Relief of pain has been reported following the use of stilbamidine, however since this drug is very toxic and its effectiveness in multiple myeloma is uncertain its value in this disease is doubtful. Urethane is occasionally of value, but its effects are usually not seen until after four to eight weeks of treatment and only a small proportion of patients exhibit a good response. Corticotropin and the corticoids provide temporary beneficial effects in about half the cases of this disease.

BRONCHOGENIC CANCER

In cases in which radiation is inadvisable or must be postponed nitrogen mustard or TEM can often be used advantageously. Relief of pain, cough and dyspnea are frequently achieved. The effectiveness of chemotherapy is usually of short duration and it must consequently be considered as a temporary although important part of the management of bronchogenic cancer. Corticotropin and corticoids are of special palliative value in improving the airway and decreasing edema, bronchial secretions and spasm.

CANCER OF THE SKIN

Chemotherapy can often provide relief of pruritus and regression of the lesions of mycosis fungoides and

are being obtained in certain cases of acute leukemia in adults with doses of 1 Gm daily for 10 days followed by maintenance doses of 50-100 mg daily. The duration of such remissions has yet to be determined. Some investigators have used up to 5 Gm daily. This drug in doses of 100 mg a day or less also produces great palliation in certain cases of intracranial metastases.

Large doses and prolonged therapy with all of these drugs produce Cushing's syndrome with sodium retention, potassium loss, insomnia, peptic ulcer, nervousness, euphoria and occasionally mental disturbance. Derangements of protein synthesis and carbohydrate metabolism, depression of the thyroid, amenorrhea and osseous decalcification may occur, and the physician must be alerted to these effects and reduce the dose as indicated. Abrupt cessation of therapy with any of these drugs will produce acute although temporary adrenal insufficiency.

ANDROGENS

The choice of androgen in the treatment of cancer depends to some extent on which route of administration is preferred. The dose of methyltestosterone is 100 mg per day orally in women who have cancer of the breast. Methyltestosterone has been reported to produce hepatitis and this may contraindicate its use in some cases. Testosterone propionate is given intramuscularly in doses of 50-100 mg three times weekly. Androgen therapy should be continued for 8-10 weeks in order to ascertain its effect. Androgens will usually provide a sense of well being and may often bring

palliation in terminal states of any type of malignancy, reducing hyperpyrexia, nausea vomiting anorexia and anemia. Sometimes it appears to be of greater value than the corticoids.

CORTISONE ACETATE is useful in the same condition as corticotropin. The initial dose of cortisone acetate is usually 200-300 mg a day, with gradual reduction to 75-100 mg for maintenance therapy. Its action is more rapid but less prolonged by mouth than by the intramuscular route.

HYDROCORTISONE administered in about two thirds the dose of cortisone has the same physiologic reactions as cortisone and is effective orally. The anti-inflammatory reaction may occur a little more rapidly. This corticoid is available in alcohol solution for intravenous therapy. For rapid cortical effect 100 mg of hydrocortisone in 50 cc alcohol is diluted in 500-1000 cc of 10 per cent dextrose and given by vein over a four to six hour period. The concentrated alcohol solution must never be given undiluted.

PREDNISONE (Meticorten Deltasone Delta) is effective in the same conditions as corticotropin, cortisone and hydrocortisone but has the advantage of having less effect on the mineral metabolism and therefore can be given in relatively higher therapeutic doses without producing as profound changes in sodium and potassium metabolism. Nonspecific palliative effects can be obtained in metastatic cancer with doses of 20-50 mg daily. It appears to be the steroid of choice in lymphomas frequently controlling these diseases for months with 40-100 mg daily. Promising results

per cent solution of sodium citrate may be used to control a runaway hypercalcemia. Corticoids are also useful in hypercalcemia, and 200 mg cortisone (or its equivalent) daily can be employed. In the female estrogens usually provide a sense of well being but the physician must nevertheless be alert for those instances in which these hormones provoke an exacerbation of the malignancy. The abrupt cessation of therapy will produce uterine bleeding in any female regardless of age. In the male these hormones will provoke loss of libido and painful gynecomastia.

FOLIC ACID ANTAGONISTS

The two most commonly used agents in this class are AMINOPTERIN and METHOTREXATE (also known as amethopterin). The usual oral or intramuscular dose of aminopterin is 0.25–0.5 mg and that of methotrexate, 2–5 mg. The drugs are given three to six times weekly and can produce dramatic hematologic changes. Daily studies of the blood and hematopoietic system are prerequisites to the proper use of these agents in the early stages of treatment. Later when the hemogram is stabilized these observations may be reduced to once or twice a week. The more serious reactions to these agents are leukopenia and hypoplasia of the bone marrow. Lesions of the mucous membranes are an early sign of impending difficulty. Bleeding in the gastrointestinal tract is usually but not always preceded by diarrhea. In any event, diarrhea should be a sufficient basis for cessation of treat-

about an increase in body weight. They produce a retention of sodium, and the resulting edema may provoke congestive heart failure. Hypercalcemia may also occur especially in patients with osteolytic metastases. The untoward effects of androgen therapy in women include hirsutism, deepening of the voice, acne, enlargement of the clitoris and an increase in libido which may be severe enough to produce eroticism. Masculinization of women may appear with doses of testosterone propionate as small as 100 mg per month. The so called 'androgens of low androgenicity' are of no greater value in cancer of the breast since the effective dose must be large enough to produce virilism similar to that resulting from testosterone propionate.

ESTROGENS

Diethylstilbestrol and ethinyl estradiol have the advantages of high potency, oral effectiveness and relatively low cost. The usual dose of diethylstilbestrol is 15 mg daily, and that of ethinyl estradiol approximately 3 mg daily. These doses are 15-30 times larger than those used for replacement therapy. The common side effects of estrogens include nausea, emesis and anorexia. More serious are edema and hypercalcemia which may occur as the result of continuous administration of estrogens. Rising calcium levels in the blood should indicate the need for prompt discontinuation of estrogens and measures should be taken to insure an adequate fluid intake. As an emergency device the intravenous administration of 250-500 cc of a 2.5

MYLERAN

Myleran (1, 4 dimethanesulfonylbutane, known experimentally as G T 41) is one of the more promising new agents in the treatment of leukemia. It is effective orally and appears to be more selective in its action on myeloid cells than nitrogen mustard or the folic acid antagonists. It is particularly useful in those cases of chronic myelocytic leukemia which have failed to respond to radiation therapy. It has a relatively rapid onset of action and produces minimal effects on the lymphocytes and platelets except when large doses are used. Careful hematologic studies should be made daily during the early stages of treatment and at least once weekly thereafter. Myleran should be discontinued if there is evidence of depression of bone marrow function. If there is a sudden drop in the leukocyte count during the initial treatment with Myleran the drug should be withheld until the nadir is reached. Therapy can be reinstituted when the white blood cell count begins to rise. Oral doses of 2-8 mg daily have been used to produce the desired decrease in the leukocytes which is usually well developed after about three weeks of treatment. The duration of the remission may be as long as 12 months and repeated courses of therapy have been used to advantage. The toxic effects of overdosage are thrombocytopenia and hypoplasia of the bone marrow. Unlike the folic acid antagonists there is no specific antidote.

ment with these agents Thrombocytopenia also may be so severe as to warrant discontinuation of therapy Alopecia sometimes occurs with long term therapy The term "folic acid antagonist" is perhaps unfortunate but it is entrenched in the literature and there would be little use in disputing it at this time That these agents do *not* act as antagonists to folic acid in man has important clinical significance The drugs act as antimetabolites by preventing or interfering with the conversion of folic acid (pteroylglutamic acid) to folinic acid (citrovorum factor) Therefore, it follows that folic acid is of no value as an antidote to the toxicity of aminopterin or methotrexate Folinic acid (citrovorum factor) on the other hand is an effective antidote Unfortunately, the administration of folinic acid although it counteracts the toxicity of these agents also negates their effectiveness in the treatment of leukemia

FOWLER'S SOLUTION

Fowler's solution (potassium arsenite solution N F) is used in the treatment of chronic myelocytic leukemia Its use is based on the depressing effects of inorganic arsenic on the formation of white blood cells The toxic effects of Fowler's solution are accordingly the same as those of arsenic Consequently any consideration of its use must involve a comparison with the effectiveness and toxicity of other chemotherapeutic agents such as Myleran

intra arterially Nitrogen mustard is given in single doses of 0.1 mg/kg b.i.d. for 2-3 days or once daily for 4-6 days Thus, the total dose in either schedule is 4-0.6 mg/kg Giving 25 mg chlorpromazine (Thorazine) orally one hour before the administration of nitrogen mustard helps to prevent nausea and emesis

URETHANE

Urethane (ethyl carbamate) is unlike nitrogen mustard and some other chemotherapeutic agents in that it does not have any special affinity for rapidly proliferating cells It resembles the other agents, however in producing the desired depression of bone marrow function Its effects are sometimes so rapidly progressive that an aplastic bone marrow (with severe leukopenia and anemia) may require immediate cessation of therapy The sedative characteristics of urethane are usually not troublesome except in ambulatory patients Nausea, emesis, vague gastrointestinal discomfort and hepatic damage have been reported Urethane is given orally in the form of enteric coated tablets in order to minimize the local gastric irritant properties of the drug The usual dose in leukemia is 1 Gm t.i.d. until the leukocyte count falls to about 20,000 In multiple myeloma the dose is 1-2 Gm t.i.d. until the desired result is achieved (usually 4-8 weeks) The low cost of urethane, the ease of administration, and its effectiveness in relieving fever, skeletal pain and hematologic abnormalities make it a desirable agent

NITROGEN MUSTARD

The cytotoxic effects of nitrogen mustard (mechlorethamine NF Mustargen) are very similar in many respects to those of radiation. Therefore careful hematologic studies should be made before giving nitrogen mustard after radiation therapy, or vice versa in order to make certain that sufficient time has elapsed for recovery of bone marrow function. Within a day or two following the administration of nitrogen mustard a lymphocytopenia occurs which becomes maximal in about a week. The leukopenia, thrombocytopenia and depression of bone marrow function limit the dosage of nitrogen mustard during any course of therapy. Granulocytopenia and a decline in both the red blood cell count and hemoglobin are characteristic consequences of therapy with nitrogen mustard. Nausea, emesis, amenorrhea and depression of spermatogenesis are among the other common reactions. Nitrogen mustard is a vesicant agent and its local toxicity is such that a special technic must be used for its administration. The drug is usually given intravenously with every precaution taken to prevent its leakage into the subcutaneous tissue where it would produce sloughing. A rapid flow of saline solution is introduced intravenously, if there is no evidence of leakage the flow is stopped temporarily while the nitrogen mustard is injected and then is again given at the previous high rate for a few minutes. In some cases it is possible to focus the effect of nitrogen mustard on a specific tissue by injecting the drug

some promise of being a relatively safe and useful agent. These compounds are chemically, and in some ways pharmacologically, related to nitrogen mustard and TEM. ThioTEPA appears to be effective orally and can be given by intravenous or intramuscular injection without danger of venous thrombosis and with little or no nausea or emesis. The limiting factors are the same as those of nitrogen mustard namely, leukopenia, thrombocytopenia and depression of bone marrow function. Therefore it is recommended that hematologic studies be made daily during the early stages of treatment with ThioTEPA and at least once weekly during maintenance therapy. The dosage of ThioTEPA in chronic leukemia varies according to the hematologic findings and the clinical requirements. Harry Shay *et al* (AMA Arch Int Med 92:628, 1953) used 2 \square or 10 mg intramuscularly. The total dose varied from as little as 28 mg to more than 500 mg. In chronic leukemia ThioTEPA \square given as needed until the desired hematologic response occurs, the minimal effective maintenance dose is used thereafter. It is recommended that the patient receive a high fluid intake. There have been conflicting reports of the usefulness of ThioTEPA in solid tumors.

6 MERCAPTOPURINE

This drug (Purinethol) acts as an antagonist to hypoxanthine and adenine and is thus an antipurine. It differs from the folic acid antagonists both by its mechanism of action and by the fact that there is no

TRIETHYLENE AMINE (TEM)

TEM is considered to have the same type of cytotoxic action as that of nitrogen mustard. It has significant advantages, however, in that TEM is effective orally and produces less nausea and emesis than does nitrogen mustard. The absorption of TEM from the gastrointestinal tract is somewhat erratic, however, absorption can be facilitated by the simultaneous administration of sodium bicarbonate. Oral dosage schedules range from 5 mg daily for from 2 to as many as 10 successive days. Two grams of sodium bicarbonate are usually given orally with each 5 mg dose of TEM. It is important to note that the maximal effect of TEM usually occurs about 10 days after initiation of therapy, therefore time should be allowed for these effects on the bone marrow to be assessed before starting a new course of therapy or continuing the administration of TEM. This delay in the onset of action makes TEM less desirable than nitrogen mustard in cases where a rapid effect is needed. The systemic toxicity of TEM and the precautions attending its use are in general the same as those of nitrogen mustard.

ETHYLENE PHOSPHORAMIDE DERIVATIVES

Three of the ethylene phosphoramidate derivatives which have been studied clinically are DEPA (diethylene phosphoramidate), TEPA (triethylene phosphoramidate) and ThioTEPA (triethylene thiophosphoramidate). Of these three ThioTEPA seems to have

A Cancer Res 21 1955) reported on the use of OPSPA in more than 100 patients with solid tumors who were observed for periods of 1-18 months. The drug was given either intramuscularly, into serous cavities or directly into the tumor. There was some evidence of temporary palliation which should encourage further investigation of the use of this agent. Like the other ethylene phosphoramide derivatives OPSPA can produce a severe leukopenia.

Studies in animals are being carried out with many other chemical compounds some of which are under going clinical trial. Among these are agents such as azaserine, demecolcin, β -thioguanine, azaguanine and desoxypyridoxine.

known antidote to 6-mercaptopurine. It is important that complete hematologic studies be made daily during the initial stages of therapy and at least once weekly thereafter. Since the maximal effect on the hematopoietic system may be delayed for several days the drug should be discontinued temporarily at the first sign of a precipitous fall in the white blood cell count. Toxicity arising from overdosage includes hemorrhage, leukopenia, anemia and thrombocytopenia. Dosage of 6-mercaptopurine must be adjusted on the basis of the hematologic and clinical findings. Usually, 2.5 mg/kg per day orally is the initial dose. If after one month of treatment there is no evidence of depression of the leukocytes and no clinical improvement the dose is increased up to 5 mg/kg daily. If the leukocyte count falls the drug should be discontinued and after the count has remained constant for several days or begins to rise a suitable maintenance dose should be initiated. It should be remembered that unlike some other chemotherapeutic agents 6-mercaptopurine *must* be given in maintenance dosage if an early relapse is to be prevented. It is best to seek the minimal effect dose of this drug at all times and especially in those patients with impaired renal function.

EXPERIMENTAL AND MISCELLANEOUS AGENTS

OPSPA (oxapentamethylenediethylene thiophosphoramidate) is a recent addition to the ethylene phosphoramidate derivatives. A. R. Curren *et al* (Proc Am

surgeon who is capable of relieving the patient's pain by an operative procedure. The two procedures obviously go hand in hand and represent a form of medical teamwork.

The general surgical procedures discussed here are those that are used primarily in dealing with patients afflicted by a malignant disease that has reached an advanced stage. The operations mentioned do not in any sense constitute definitive therapy of any specific cancer. The discussion is confined to certain procedures which may extend life and alleviate pain and discomfort of incurable neoplastic disease.

GENERAL CONSIDERATIONS

Before attempting to analyze special situations calling for surgical intervention in the care of patients with advanced cancer certain basic considerations should be reviewed. They are common to practically all patients with this form of illness and they form the background in which the surgeon develops the tactical approach which he must apply to the treatment of his patient.

TYPE OF NEOPLASM—Cancer must usually be considered in the category of chronic rather than acute illness. This is true even of the far advanced cancer no longer amenable to definitive therapy as well as of the early neoplasm. The degree of chronicity, however, depends on many factors. The most important is the histological type and biological characteristics of the specific neoplasm. This can best be illustrated

CHAPTER 5

Surgical Procedures in Control of Pain in Advanced Cancer

AN OLDER PHYSICIAN used to admonish his residents
Cure some help many comfort all At no other
time in the practice of medicine can the physician
apply this advice more aptly than when he is treating
a patient suffering from cancer that is incurable from
its outset or for which treatment has failed

Before embarking upon a discussion of specific procedures that may be applied to situations created by malignant disease it is necessary to realize that the surgeon is but one member of a medical team available to treat the pain and distress of patients with advanced cancer Any efforts on the part of the surgeon to help his patient must be carried out within the framework of the capabilities of the entire medical team For example it would seem ill advised indeed to prolong the life of a patient who is suffering from advanced cancer of the cervix limited to the pelvis by diverting the urinary stream if one failed to take into consideration one member of the team a neuro

EXTENT OF LESION—The estimation of the local anatomic extent of a neoplasm and of the presence or absence of metastases, even though not absolute, gives some insight into the patient's prospect for continued survival. Cancer may destroy its host in many different ways. Local extension of the primary lesion regardless of its metastases may destroy some organ or function that is vital to the patient's bodily economy. By metastases, a cancer may reach the same end point and there are other ways in which the parasitic growth overwhelms the bodily economy of the host on a quantitative basis. Obviously, then, the greatest palliation and extension of life may be expected in instances in which the tumor is destroying its host through its local effect. Advanced tumor limited to the pelvis is an excellent example of such a situation. Many patients die of advanced cancer of the uterus or prostate without evidence of extension of the neoplasm outside the anatomic confines of the pelvis. Death from cancer limited to the pelvis not infrequently occurs in rectal and bladder cancer although this is not as common as in prostatic and uterine cancer. In all these instances obstruction of the urinary excretory system at the lower third of the ureters contributes heavily to the mortality rate. Since all of these lesions tend to produce obstructive hydro-nephrosis with pyelonephritis, kidney failure with uremia is a fairly common cause of death. Pain is similarly a common problem in that by local extension the sciatic plexus of nerves very shortly becomes involved in tumor. There are surgical methods to correct

by means of the survival curves of patients who have various types of cancer but are treatable. Failure of specific therapy in curable cases gives us a fair picture of some of the characteristics of various cancers. In some cases failure is prompt as is death from failure; in others failure occurs and is sustained over a long period of time. It is known, for example, that patients with incurable breast cancer usually die within the first two years after the diagnosis was made. However, a surprising number of patients whose breast cancer has been deemed incurable continue to survive even longer than five years—the yardstick familiar to all who treat cancer. On the other hand, most melanocarcinomas when inoperable are fatal within 12 months. This disease then is apparently less chronic in its evolution than is breast cancer. Again there are patients who have survived amazing lengths of time with known incurable melanocarcinoma. As a larger number of tumors are studied in this manner, it becomes fairly evident that each specific histological type of lesion has a natural history of its own determined primarily by its biological characteristics. Each has predilections as to the anatomic sites at which the primary tumor arises. Each specific tumor has some characteristic manner in which it metastasizes as well as a manner in which it produces local destruction. Unfortunately at this time we are unable to predict accurately the biological growth characteristics of any given tumor; furthermore we are unable to select the individual who is destined to survive any appreciable length of time whether treated or not.

damage complicate the patient's problem the surgeon might in the face of incurable disease be justified in choosing the simpler operative procedure. This type of reasoning would not, however, apply to a patient with clinically curable rectal cancer even though his problem was complicated in the manner just described. The final decision in balancing the general physical status of the patient with the proposed operation must rest primarily on the surgeon and be governed by his experience. Since there is no exact guide to such decisions the evaluation of risk in a patient can usually be summed up in the simple statement "What is best for the patient is best for the doctor."

ATTITUDE OF PATIENT—The attitude of the patient to any situation created by the disease varies tremendously. It is given direction and impetus by numerous factors many of which are immeasurable. They are more thoroughly evaluated in Chapter VII. Attitude is mentioned here only as it relates to the employment of surgical therapy. In the long run the final answer to any surgical problem is the patient's clear understanding of the situation and his acceptance or rejection of the surgical plan of treatment.

The preceding paragraphs outline in the general way the key factors which a surgeon must consider in deciding on a course of treatment for his patient. The procedure must offer some degree of alleviation of the patient's symptoms either as a result of the operation itself or in conjunction with some other form of therapy. The relief of pain of course is of paramount importance. However the relief of any form of dis

both of these difficulties and achieve extension of life and relief of pain in a fair number of these patients

TYPE OF DISABILITY—Death from any specific type of cancer is indeed protean. It usually occurs when some vital function or functions are destroyed. Even though a tumor is far advanced and incapable of cure it is often possible for the surgeon to restore or substitute for some vital function that is becoming lost to the disease and to postpone death at least temporarily. Intestinal obstruction that results from the invasion of the bowel by a neoplasm is an excellent example. In this case, simple surgery gives much relief.

GENERAL PHYSICAL STATUS OF PATIENTS—It has often been said that there are few if any medical contraindications to the treatment of cancer. This statement applies primarily to those lesions which are amenable to definitive attack and provide the patient with the hope of a reasonable chance for survival. However, this attitude is not generally applicable to the individual in whom a malignant neoplasm has developed to the point where death is inevitable. In such a case the physician must make a serious effort to evaluate the possible rewards of a surgical procedure against the poor outcome of treatment which might result from the presence of some secondary complicating organic illness. Not infrequently this problem arises in connection with rectal cancer. Even in the presence of hepatic metastases patients live on the whole as long and most assuredly more comfortably after an abdominal perineal resection of the rectum than after a simple colostomy. But should extensive cardiac

chest tend to produce respiratory obstruction (1) tumors that are primary within the tracheobronchial tree (primary bronchogenic cancer), (2) far advanced cancer occurring within the lower portion of the upper third or the middle third of the esophagus and (3) tumors arising primarily in the mediastinal lymph nodes (as, for example, lymphomas) or as the result of metastatic cancer in the mediastinal nodes particularly in the region of the pulmonary hilus. Respiratory obstruction has occurred as the result of metastatic disease in the mediastinal lymph nodes secondary to primary lung, esophageal and breast cancer, to cite but a few examples. When respiratory obstruction results from cancer within the thorax, the surgeon is at a loss to supply the patient with any adequate airway. Although there are reports that airways have been provided surgically through the thoracic wall, these operations have usually been done after trauma to the thorax with injury to the tracheobronchial tree rather than in an effort to relieve the obstruction produced by a malignant neoplasm within the chest. Most respiratory obstruction at this level that is caused by cancer results not so much from extrinsic pressure on the tracheobronchial tree as from direct invasion of this structure. Hence the decompression operations (sternotomy) that have been carried out with some degree of success in rapidly expansile lesions within the chest (that is, aortic aneurysm) are not applicable to the treatment of invasive cancer. Little or nothing can be accomplished by surgical techniques to relieve the respiratory obstruction within the chest that is

comfort—for example asphyxia hunger thirst intestinal cramping nausea or vomiting—is about on a par with relief of pain. The ability of an operative procedure to extend life so long as that life remains comfortable is also to be desired, but no physician is required on moral grounds to extend the life of a patient which when extended, would only make the patient more miserable. The only situation that demands this heroic form of treatment must arise at the specific request of the patient. The operative risk of any contemplated surgical procedure must be estimated, and this estimate must be presented to the patient when the proposed procedure is discussed in order that he may apply it to his scale of values in either accepting or rejecting the advice of his surgeon.

SPECIFIC SITUATIONS REQUIRING SURGICAL INTERVENTION

RESPIRATORY TRACT

Obstructions of the respiratory tract that result from invasive cancer are conveniently divided into two main groups. The first consists of obstructions that arise within the thorax below the suprasternal notch. The second group consists primarily of tumors that involve the respiratory tree above this point. This division is actually not quite this arbitrary since the surgeon is usually unable to relieve respiratory obstruction within the thorax but can restore an adequate airway when obstruction occurs within the larynx or above it.

Three major groups of tumors occurring within the

out this procedure is an elective operation. Urgent tracheotomies are best done under local anesthesia, however, as a lifesaving procedure when time is an important factor, anesthesia is not necessary. The hypoxia produced by the respiratory obstruction in such emergencies tends to dull the patient and acts as an anesthetic by itself.

Every physician should be capable of carrying out a tracheotomy when the occasion arises, for the procedure is simple. After proper preparation and local infiltration of 10 per cent procaine (time for this should not be wasted in urgent situations) a simple longitudinal incision is made in the midline of the neck and carried down through the ribbon muscles above the isthmus of the thyroid. The lower border of the cricoid cartilage and the first three tracheal rings are exposed by the division of the pretracheal fascia. The second or third tracheal ring is grasped by a fine sharp hook and a linear incision is made to divide the second and third tracheal ring opening the airway. A small block of cartilage is excised from each of these rings to assure a patent airway. A tracheotomy tube with its obturator is then inserted into the trachea and the obturator removed. The tube is tied in place around the neck and the incision is closed by interrupted black silk sutures in anatomic layers to close the skin around the tracheotomy tube. This airway is kept clean by means of intermittent suction when ever necessary. In extremely urgent situations it may be necessary as a preliminary measure to insert a large no. 13 gauge needle into the trachea or to thrust

caused by primary or metastatic cancer. Such relief remains a problem for the radiotherapist.

Above the level of the suprasternal notch the encroachment of a cancer upon a patient's airway becomes another problem, but by and large obstructions in this area can be handled in a satisfactory manner. Obstruction usually occurs as it does within the thorax, by direct invasion of the tumor, and this invasion gradually obliterates the airway by the very bulk of the tumor rather than by pressure effects. Most frequently obstruction is caused by a primary epidermoid cancer arising within the larynx, but far advanced lesions of the base of the tongue and of the hypopharynx may also obliterate the airway. Cancers within the oral cavity or nasopharynx seldom produce an obstruction of such severity that the patient's airway is in actual danger. Occasionally primary cancers arising in the thyroid or parathyroid may invade the trachea and cause respiratory obstruction; however, this is not the usual course of these neoplasms. Only rarely do cervical lymph nodes that have become involved, either in primary tumors of lymph node origin or in metastatic cancers, enlarge sufficiently and invade the larynx or trachea to produce obstruction.

It is quite feasible to short circuit the respiratory passages by means of a tracheotomy. Occasionally this procedure must be carried out as an emergency when respiratory embarrassment jeopardizes the patient's life. In ordinary circumstances, however, the gradual development of stridor and progressive dyspnea provide an adequate warning. It then becomes possible to carry

swallow his own secretions represents the lesser of the two evils. Ideally, the ultimate in palliation is achieved by resection of the offending lesion. However, when this cannot be accomplished because of a nonresectable lesion, resort must be made to some other device. Oftentimes even though the hypopharyngeal and esophageal cancers are inoperable and incapable of cure, radiation therapy will make it possible for the patient to swallow and do much to relieve the pain and discomfort at least temporarily.

Within the oral cavity, lesions involving the floor of the mouth, gingiva, buccal mucous membrane and tongue can, if uncontrolled, severely upset a patient's nutrition and fluid balance. In this situation, there is no actual mechanical obstruction, but invasion of the oral and pharyngeal musculature makes mastication and swallowing mechanically difficult and extremely painful, and this is a terrific deterrent to an adequate intake of food and water.

Lesions arising in the oropharynx can usually be circumvented by the simple insertion of a plastic nasal feeding tube. Recent improvements in the types of feeding tubes available and of tube feedings make it possible to sustain a patient comfortably for weeks and even months if necessary. Extension of the patient's life in this manner will provide the time needed for other members of the medical team to achieve relief of pain. In lesions which obstruct the digestive tract at the hypopharynx or below, it is usually not possible to pass such a feeding tube and consequently some sort of operative procedure must be car-

a trocar into the trachea to provide adequate ventilation while equipment is being secured to carry out the tracheotomy

UPPER DIGESTIVE SYSTEM

Lesions producing obstruction in the upper digestive system occur most frequently from the level of the hypopharynx to the pylorus of the stomach. In the hypopharynx and esophagus these cancers are usually epidermoid in character. They may occur anywhere within the anatomic region but are seen most frequently in the lower third of the esophagus next in order of frequency at the level of the hypopharynx then in the upper third and finally in the middle third. In the stomach adenocarcinoma located either at the cardioesophageal junction or at the pyloric outlet are the primary offenders so far as the production of obstruction is concerned.

The most miserable symptoms of an obstruction of the upper digestive system are dysphagia, regurgitation, nausea and vomiting, sticking pain within the chest and aspiration of gastrointestinal contents into the tracheobronchial tree as a result of vomiting or regurgitation. People who are unable to swallow either food or liquids perish very shortly unless a substitute is provided to circumvent the inability to maintain their nutrition and fluid and electrolyte balance. Trouble also arises from the inability of these individuals to swallow their own secretions from the respiratory tract and the salivary glands. However, if nutrition can be maintained the patient's inability to

tumor infiltrating the stomach wall. This operation makes it possible for the patient to resume eating and drinking in a normal manner. However, in instances of stomach cancer in which the obstruction is at the region of the pylorus and the stomach is diffusely infiltrated by cancer, it is impossible to perform a gastrojejunostomy. It is then necessary to utilize the small bowel as the site into which fluids and feedings are administered. In the extremely poor risk patient, a simple Witzel type of jejunostomy may be performed. The jejunostomy should be done as close to the ligament of Treitz as is technically feasible in order to utilize the largest possible absorbing surface of the small bowel. In the better risk patient the divided Roux Y type of jejunostomy may be carried out with anastomosis of the upper portion of the divided bowel in an end to side fashion with the jejunum below. The portion of the Y to be carried out as a jejunostomy must exceed eight inches in length. Segments of bowel shorter than this facilitate the regurgitation of bowel contents through the ileostomy stoma and such regurgitation causes marked skin excoriation which can become quite troublesome. If the feeding loop is long enough regurgitation is never much of a problem. Some caution must be used in both the speed of administering the tube feedings and their concentration when introduced into the small bowel. Concentrated feedings cannot be tolerated initially and are usually followed by diarrhea and cramping. In some instances when administered fairly rapidly these feedings produce symptoms similar to the dumping syndrome that

ried out to alleviate the patient's inability to swallow

Lesions producing obstruction at the level of the cardioesophageal junction or above can be circumvented by means of a simple gastrostomy. Many types of gastrostomies are described in the standard operative texts. However the simplest type, a Stamm gastrostomy can be carried out with very little operative trauma. The operation may be readily completed utilizing intercostal block and infiltration type of anesthesia and will provide for many months a stoma adequate for the nutrition of the patient. The procedure is usually carried out through a left rectus muscle-splitting incision placed high in the left upper quadrant. A stab wound is made in the anterior wall of the stomach through which is passed a large Pezzer catheter. Three concentric purse string sutures are placed about the catheter and tied. The anterior wall of the stomach is anchored to the parietal peritoneum by means of interrupted sutures. The abdominal incision is closed in anatomic layers about the catheter. A sterile dressing is applied and usually within 12-24 hours fluids may be given through the new opening. This type of gastrostomy functions as well in most cases as the more complicated varieties.

In cancer of the pylorus of the stomach which is still limited to the area but locally nonresectable to maintain the continuity of the gastrointestinal tract it is best to by pass the tumor by means of a gastroenterostomy. The location of this short circuiting operation depends largely on the region of the stomach which is most dependent and yet well away from

(when metastases have occurred either to liver or to peritoneum, or the primary tumor has directly involved other viscera or the abdominal wall), the lesion still develops slowly and much can be done to prolong a patient's life and make existence more comfortable. With knowledge of the behavior of this type of cancer it then seems best to resect the primary lesion, whenever possible. This should be done not only because these lesions produce intestinal obstruction but also because they are a constant source of chronic blood loss and infection, complications which take their toll by gradually sapping the patient's general physical condition and sense of well being. If because of the extent of the primary lesion it is not possible to excise it the gastrointestinal tract must then be diverted.

In the case of obstruction of the distal half of the large bowel (left colon and rectum), a colostomy is required. Because of the fluid conserving function of the colon when a diversion of the large bowel is necessary as much unaffected bowel must be spared as possible in an effort to produce a colostomy that can be adequately controlled. The so called "wet colostomy" leaves much to be desired both from the physician's and the patient's point of view. Where colostomies are used to divert the fecal stream as a permanent measure the completely divided type of colostomy is by all odds preferable to the simple loop type. The former eliminates the possibility of spillover of fecal material into the distal loop and more effectively defunctionalizes the bowel distal to the colostomy site.

follows subtotal gastric resection. However, if nutritive solutions are started slowly, these complications can usually be avoided or at least minimized.

LOWER DIGESTIVE SYSTEM

Dysfunction of the lower digestive tract produced by advanced cancer implies intestinal obstruction, although occasionally the development of an intra abdominal abscess with the formation of fecal fistulas heralds the presence of far advanced bowel cancer. Simple mechanical intestinal obstruction is encountered more frequently, however, than any other single complication in tumors arising in this anatomic location and an obstruction from advanced cancer in the lower digestive tract usually implies a cancer of the large bowel. Although primary tumors of the small bowel are infrequent, small bowel obstructions sometimes occur in the late phase of large bowel cancer or cancer of other intra abdominal viscera and usually result either from the direct invasion of the small bowel by such a lesion or from the progression of peritoneal implants.

No matter what the cause of intestinal obstruction, there are certain principles which the general surgeon must keep in mind when dealing with this problem. Large bowel cancer is noted primarily for its slow local development and slow progression from onset to termination. Indeed, in many instances, months elapse before there is any evidence of metastases from such a cancer. Even in the late phase of a patient's illness

may occur either as a manifestation of a primary tumor or secondarily from involvement of the small bowel by cancer arising at another site. Again, whenever feasible, maximum palliation may be obtained from the resection of the lesion that has produced the obstruction. When this is not possible a short circuiting operation should be carried out to restore the continuity of the intestinal tract. This can be done either by totally defunctionalizing the small bowel involved or, more simply by making a side to side enteroenterostomy. In this situation the anastomosis acts very much like a penny put in a fuse permitting overflow into the unaffected small bowel below the site of obstruction. Rather large segments of small bowel may be defunctionalized without any permanent effect on a patient's nutritional status. Because of the shortened small bowel diarrhea may occasionally result, but usually it is only temporary and can be controlled by medical and dietary management.

LIVER

There is no worthwhile palliation to be gained from the surgical treatment of primary liver cancer or metastatic cancer involving the liver parenchyma. The only exception is in the treatment of solitary hepatic metastases or solitary primary lesions of the liver which are found to be technically resectable.

Extrahepatic biliary obstruction can be relieved surgically. Of the tumors that produce obstructive jaundice cancer of the head of the pancreas is the most frequent with primary carcinoma of the extrahepatic

When obstruction occurs in the ascending colon or cecum and if the lesion is nonresectable it becomes necessary to by pass this area by means of a sidetracking operation. This is most usually accomplished with an ileotransverse colostomy. As in the case of the distal colon, it is better so far as the patient is concerned to divide the bowel proximal to the lesion to make a complete diversion of the gastrointestinal tract. This is usually carried out as an end to side ileotransverse colostomy and the distal segment of the terminal ileum is brought out to the abdominal wall to form a mucous fistula. This complete diversion of the fecal stream from the region of the tumor tends to reduce infection and recurring blood loss. A cecostomy should be reserved only for the decompression of an obstructive lesion in the ascending or transverse colon which can be treated in a definitive manner at a second operation. A cecostomy is ineffective as far as the complete and permanent defunctionalization of the bowel is concerned and if used for this purpose proves unsatisfactory. The cecostomy will work only so long as the obstruction is complete and the bowel proximal to the obstruction is filled with fecal material. The patient will usually continue to have some degree of symptoms in addition to the trouble of controlling the liquid fecal material that extrudes from the cecostomy. When it is not feasible to divide the small bowel completely a certain degree of defunctionalization may be obtained from a wide side to side ileotransverse colostomy.

As previously pointed out small bowel obstructions

the patient's fluids and electrolytes and this loss must be compensated by the ingestion of either the bile that is lost or animal bile substitutes. From the standpoint of operative safety, however, cholecystostomy represents the least traumatic of all the decompression operations. Biliary shunts can be made from the gallbladder to the stomach to the duodenum or to a loop of jejunum. In most instances though it is not desirable to use the gallbladder to drain obstructive jaundice caused by cancer particularly if the short circuit is to be permanent, for as time goes on, the neoplasm that produced the initial obstruction sometimes extends to involve the cystic duct obliterating the shunt. Jaundice then recurs.

When a lesion is located in the head of the pancreas it is more desirable to divide the common duct and reanastomose the proximal end into one of the nearby hollow viscera. The most satisfactory approach is the anastomosis of the common bile duct into a defunctionalized loop or limb of jejunum. Again, as in the feeding jejunostomy this limb should be long enough to prevent the regurgitation of gastrointestinal contents since regurgitation, if it occurs tends to cause repeated episodes of ascending cholangitis. This condition can be eliminated by making certain that the limb used to drain the common duct is adequate in length. These anastomoses are usually carried out in two layers using interrupted black silk sutures throughout. The reanastomosis of the proximal end of the common duct into the duodenum although quite effective in relieving the obstruction occasion

biliary tree, the gallbladder and the ampulla of Vater following in order of frequency. Other cancers arising in this immediate anatomic area have also been noted to produce this distressing symptom, these include stomach cancer, primary duodenal cancer and in one particular case lymphosarcoma arising in the lymph nodes of the porta hepatis and occluding the common bile duct.

With the possible exception of cancer of the ampulla of Vater definitive types of operative procedures, such as pancreaticoduodenectomy produce little other than palliation when the effects of treatment are measured in terms of survival. Nevertheless whenever it is possible a lesion still confined to the head of the pancreas should be treated as curable cancer and resected. In the vast majority of cases the major benefit derived from this radical form of surgical treatment is the relief of the symptoms of obstructive jaundice. The symptoms of pruritus, digestive disturbances, blood clotting derangements, bleeding tendencies associated with jaundice and, finally hepatic failure itself, call for prompt and energetic surgical efforts to relieve the obstruction. This is necessary for the welfare of the patient, even though cure is impossible.

There are many ways in which such decompression of the obstructed extrahepatic biliary tree can be accomplished. The simplest of course is drainage of the biliary system by simple cholecystostomy if the cystic duct is in direct continuity with the obstructed portion of the common bile duct. But this is the least satisfactory because it produces a constant drain on

creas the obstruction may once again be relieved by simply opening the clamp on the vertical limb of the T tube. This procedure has been carried out on several patients who survived for surprising lengths of time without further jaundice and were quite comfortable during their terminal illness.

Obstructive jaundice should be relieved surgically whenever possible. However, unless the jaundiced patient is properly prepared for surgery of this type (see any standard text relating to surgical care) the mortality rate of such operative procedures is quite high. The operative mortality is also directly proportional to the length of time that the patient has been jaundiced.

URINARY TRACT

Advanced cancer arising in the kidney does not usually produce symptoms or functional derangements that are readily alleviated by surgery. In certain instances in which pain and/or secondary infection occurs it is desirable if at all possible to remove the offending kidney. This can be done for the relief of symptoms even if it is necessary to cut through the tumor. In a kidney lesion accompanied by ulceration into the kidney pelvis chronic blood loss through the urinary excretory system may be difficult to manage by means of simple blood replacement. If such a kidney can be surgically removed the necessity for repeated blood transfusions may be eliminated.

Cancer of the urinary bladder as it becomes advanced frequently requires some form of surgical in-

ally fails before the death of the patient owing to the local extension of the primary tumor

When the common bile duct is the site of the primary cancer the distended obstructed hepatic radical above the primary lesion may occasionally be used to drain the liver. In this situation the open end of the jejunal limb is simply sutured into the hilus of the liver. If the hilus is invaded it is often impossible to locate the hepatic radicals. When this occurs the left lobe of the liver may be subtotally resected thus opening across dilated portions of the intrahepatic biliary ducts. The ducts are then anastomosed to defunctionalized limbs of small bowel in much the same manner as the tail of the pancreas is anastomosed to the bowel when a subtotal pancreaticoduodenectomy is carried out. This however is a heroic procedure, usually too extensive for the far advanced cancer patient. It is commonly reserved for the patient whose extrahepatic biliary tree has been destroyed by previous surgical trauma.

One other point should be brought up. Occasionally it has been possible to relieve obstructive jaundice by simply performing a choledochostomy and literally forcing a T tube along what would be considered the normal tract of the common duct through the tumor in the head of the pancreas into the duodenum. The T tube is sutured in place and after a few days the external limb of the tube is clamped allowing bile to drain along the horizontal portion of the tube into the duodenum. Should further extension of tumor occlude the portion of tube that traverses the pan-

30 1511, 1950), is by far the most satisfactory form of urinary diversion. The anastomoses made in this operation consist of end to side ureteral ileostomies carried out by means of very fine interrupted sutures. The mucosa of the ureter is sutured directly to the mucosa of the bowel to provide complete apposition. This anastomosis is usually stabilized by a second layer of three or four interrupted very fine black silk sutures in order to take tension off of the anastomosis. This type of ureteral anastomosis produces far fewer complications in the form of ureteral strictures and secondary obstructive hydronephrosis. With the use of these ileal segments recurring episodes of pyelonephritis are fewer and the patients have far less trouble. The anastomosis of the ureters into the intact bowel, usually at the level of the rectosigmoid is attended by a much higher incidence of pyelonephritis. However when life expectancy is limited not by the anticipated ascending renal infection but rather by the cancer itself the anastomosis of the ureters into the intact bowel is certainly justified.

After the diversion of the urinary stream has been carried out it is possible to achieve further extensive palliation by radiotherapy. When radiation therapy is to be used with a view not only of relieving symptoms but actually of extending life it is desirable to use the ileal segment as a reservoir in the diversion of the urinary stream for the reasons mentioned above. From the standpoint of the patient's comfort, the ileal bladder represents the ideal in bladder substitution. The urine which flows continuously from the ileostomy

tervention to provide palliation. The major symptoms are hemorrhage with retained bladder clots, and, superimposed on this ulcerative bleeding lesion, a secondary cystitis usually develops. This combination of bleeding and infection causes symptoms that are extremely difficult to control. The most prominent of these are hematuria, dysuria, pyuria, urgency, frequency and tenesmus. When the cancer is situated in and about the trigone of the bladder, the symptoms become exaggerated and much more difficult for the patient to tolerate. In addition, obstruction of one or both ureters occurs in lesions situated in the bladder trigone and superimposes hydronephrosis and pyelonephritis on an already uncomfortable patient. The symptoms of locally advanced bladder cancer certainly demand surgical attention.

Much relief can be obtained by the surgical diversion of the urinary stream which can be accomplished in any one of several ways. In order of simplicity, so far as surgical technic is concerned, the procedures are (1) the cutaneous ureterostomies, (2) the implantation of the ureters into the large bowel, usually the sigmoid colon, (3) the diversion of the large bowel by means of a colostomy utilizing the rectosigmoid and rectum as a separate urinary pouch into which the ureters are anastomosed, and (4) the construction of an isolated loop of small bowel brought out of the abdomen as an ileostomy into which the ureters are implanted. From the standpoint of ease of care and comfort to the patient, the so-called ileal bladder as described by Bricker (*S. Clin. North America*)

that radiates into the hips and down the lower extremities in the distribution of the sciatic nerves. When the iliac lymph nodes and iliac veins become the site of metastatic cancer, progressive marked lymphedema of one or both extremities is also noted. Any or all of these symptoms of advanced cancer demand relief if possible.

The need for relief of these symptoms was recognized long ago and from this need have developed many courageous attempts to achieve palliation. These efforts were spearheaded by Brunschwig who has pioneered a large field of salvage surgery in the treatment of cancer and who is credited with the development of the operation known as pelvic exenteration. We have been using this operation or a variant for five years in the treatment of postradiation persistent cancer of the cervix. Although this procedure may be classified as salvage surgery it should be carried out only in those patients who, on exploration are found to have cancer which is definitely limited to the pelvis and which can be encompassed surgically by the removal of the entire pelvic contents. However an operation so extensive that it produces an operative mortality rate of approximately 20 per cent and results in the mutilation of a patient does not seem to be justified unless the patient stands a reasonable chance of remaining free of the disease following the surgical procedure.

When it becomes necessary to transect a tumor in order to carry out a pelvic exenteration it is far better palliation to leave the pelvic organs in place and

stoma, may be collected in a bag sealed to the skin by an adhesive that eliminates the patient's chances of wetting his clothing with urine. This bag and the ileostomy stoma are readily cared for by the patient after very little instruction.

FEMALE GENITAL SYSTEM

Of all of the variants of female genital cancer probably the most important, from the standpoint of incidence, is carcinoma of the cervix uteri. Failure of control following the primary treatment of this particular cancer produces the equivalent of advanced cancer in the female pelvis. Autopsy studies on this particular cancer have indicated that the large percentage (approximately 40 per cent) of the patients die of the disease without evidence of extension beyond the pelvis. When the disease extends locally the sequence of events is fairly predictable. In the immediate area of the cervix persistence and extension of cervical cancer often produces rectovaginal and/or vesicovaginal fistulas. Extension from this point or failure of control of the lesion in the parametrium soon results in involvement of the distal segments of the ureters. These gradually become obstructed by tumor and slowly progressing hydronephrosis with pyelonephritis develops terminating in death from uremia. In addition, failure to control cancer of the cervix out along the pelvic walls shortly results in involvement of the nerves of the sciatic plexus. The invasion of the sciatic plexus produces intense pain

advanced ovarian cancer the large primary lesion has been resected surgically, followed by radiotherapeutic efforts to control the abdominal metastases and the patients have survived for considerable lengths of time without the necessity of frequent paracentesis to relieve their symptoms.

Patients who have advanced carcinoma of the vulva frequently experience considerable relief of symptoms even when the disease is incurable provided the local lesion is adequately removed. The pain, pruritus and burning in the region of the vulva are extremely distressing. If these symptoms can be eliminated, the patient is much more comfortable during her terminal illness. The advanced groin metastases are discussed later in this chapter.

MALE GENITAL SYSTEM

The surgical removal of testicular tumors is an integral part of the diagnosis and primary treatment of testicular cancer. Hence in the terminal phases the primary tumor is of little or no consequence. It is usually the distant metastases of this particular cancer as they involve other organ systems that may require surgical intervention. The site from which the primary tumor was removed rarely creates a problem in management.

Palliation of prostatic cancer which is not resectable locally is primarily achieved by alteration of the patient's hormone balance. The rationale of this form of treatment and that of more extensive procedures such as adrenalectomy are discussed in Chapter IV.

simply divert the urinary and/or fecal stream. As in bladder cancer, the isolated ileal bladder in which the ureters are anastomosed provides the most satisfactory urinary diversion. This is true particularly when it is necessary to perform a sigmoid colostomy to divert the fecal stream in the same patient. There is little if anything to recommend the so called 'wet colostomy'. Since uremia is the usual cause of death in these patients, diversion of the urinary stream actually tends to prolong the patient's life. With the prolongation of life after the urinary and gastrointestinal tracts have been diverted for palliative purposes, it is obvious that next in the sequence of events, as far as the patient is concerned, is invasion of the sciatic plexus by the persistent cancer. This complication then becomes a pure problem of alleviation of pain which can be readily and satisfactorily controlled by a neurosurgical operative procedure or by some of the techniques available to the anesthesiologist.

When carcinoma of the endometrium becomes too extensive or treatment fails, it resembles cancer of the cervix in many ways. The approach to the problem of persistent carcinoma of the endometrium is in all respects similar to that outlined for cancer of the cervix.

The primary symptoms of advanced carcinoma of the ovary are those referable to abdominal ascites and to the ever enlarging primary intra abdominal mass. Usually surgery offers little, if any palliation of these advanced lesions. This disease is primarily a problem for the radiotherapist. However, in some instances of

activity Surgical amputation of the penis is more or less mandatory for the control of these symptoms even though the lesion may have extended, by metastases, to the point where it is no longer curable

LARGE, ULCERATED, BLEEDING TUMOR

There is a large heterogeneous group of tumors which even though they may advance beyond the point of definitive treatment because of distant metastases can still be treated with the primary object of relieving pain or other symptoms These tumors produce many and varied types of symptoms, all of which are annoying to the patient The symptoms are usually related to (1) the size of the lesion (2) the anatomic location of the lesion (3) ulceration of the skin in the region of the primary tumor, (4) bleeding from the ulcerated site and (5) infection and necrosis in an ulcerated tumor Even though the disease has progressed beyond the bounds of possible cure, these lesions should be excised whenever possible to alleviate the local symptoms and to simplify nursing care This is particularly true when the cancer not only has become large and ulcerated but also has destroyed the function of the area involved In the treatment of cancer one encounters many situations of this type but specific reference will be made to only a few

INOPERABLE CANCER OF THE BREAST—Evaluation of the inoperability of any given breast cancer is best based on Haagensen and Stout's criteria However,

However at the site of the primary prostatic cancer obstruction of the urinary outlet may occur despite the alteration of a patient's hormone balance. As a temporary measure it is occasionally feasible to insert an indwelling catheter. The bladder may then be drained at intervals or permitted to drain continuously into a leg bag. But this is usually unsatisfactory for patients do not tolerate indwelling catheters for protracted periods of time. They usually develop secondary cystitis as a result of the presence of this foreign body. More often it is necessary to provide a more adequate urinary outlet by means of a subtotal transurethral resection of the tumor. When this is not technically feasible it may become necessary to create a permanent suprapubic cystostomy to maintain an adequate urinary flow. In such instances it is possible by means of a bag similar to those used in ileal bladders to collect the urine and keep the patient dry. Occasionally the reverse of this situation occurs. When prostatic cancer involves the external sphincter of the urinary bladder the surgeon is faced with the control of urinary incontinence. Although this does not present a problem of the magnitude created by urinary outlet obstruction it is nevertheless distressing to the patient. Such a situation is usually controlled by the use of either a penile clamp or a device designed to collect the urine in a leg bag.

Penile cancer can produce extremely distressing symptoms very similar to those noted in vulvar cancer. A large ulcerated infected penile cancer is difficult to protect from the trauma of the patient's daily

and gives the radiotherapist a better opportunity to treat the patient

EXTREMITIES—Malignant neoplasms that arise in the extremities and are no longer curable can produce many disagreeable symptoms particularly if the lesion becomes large enough to cause loss of function of the extremity or becomes ulcerated and infected. It is often necessary to amputate these extremities to relieve symptoms and to simplify nursing care.

Another interesting variant of this situation relates to vulvar cancer. Patients with vulvar cancer have been encountered who were inoperable because the metastatic disease in the groin had become too extensive for the standard iliac and inguinal dissection. The lesions had progressed to ulceration of the skin of the groin and had involved the femoral nerves producing much pain. In one case a large draining sinus had developed from an infected lymph node containing cancer that originated beneath the inguinal ligament. In another case the tumor had eroded the femoral artery and the major symptom was acute recurrent hemorrhage. In both instances the use of the extremity had been denied the patient by the metastatic disease but the patient was in good general condition otherwise. Both patients underwent hindquarter amputation and obtained considerable relief from their symptoms. One survived but a few months, the other just over a year. In both cases the palliation that was achieved justified the use of this mutilating type of procedure.

only the clinical criteria should be used with no effort to study the internal mammary and supraclavicular lymph nodes by biopsy. Because much can be said in favor of the control of the primary lesion in the breast as well as the disease in the axilla even though treatment may eventually fail these criteria may be crowded a little. If clinical judgment should be in error it seems better to err by giving the patient the benefit of the operation. For patients who are inoperable because of inflammatory carcinoma or because of clinically positive supraclavicular lymph nodes which are later proved by biopsy to contain tumor x-ray therapy may be the treatment of choice. The patients with patently disseminated disease (bone metastases) may be treated by alterations in hormone balance (see Chap. IV). When bone metastases involve the vertebral column or a long bone in which a pathologic fracture might develop these local sites of metastases may be treated by x-ray therapy.

In cases of inoperable breast cancer, the local primary lesion may become quite large and ulcerated and result in pain or bleeding or both. Patients of this type are often benefited by simple amputation of the breast, as part of the palliative treatment. When the skin of the breast is involved, care must be taken to avoid transecting tumor in the course of the amputation. Occasionally it is necessary to resect a large amount of skin along with the breast and actually to graft the thoracic cage. Such surgery however provides much relief as far as the patient is concerned.

compression type of laminectomy is necessary to avert or to correct a paraplegia resulting from such a fracture of a vertebral body. Although this operation is usually classed as a neurosurgical procedure it should be included in the armamentarium of every well trained general surgeon since time is very important in the prevention of paraplegia.

Pathologic fractures of the long bones may be given marked stability and the patient relieved of pain and deformity by the insertion of an intramedullary nail through the fracture. True the passage of such a nail through a fracture of this type tends to disseminate the tumor along the course of the medullary canal but the stability given the fracture by such a nail outweighs the risk of such dissemination. In addition it may be possible for the radiotherapist to treat the area involved. Sometimes a marked amount of recalcification and bone deposition is noted following such treatment. This type of operative procedure simplifies nursing care since large bulky plaster bandages and splints or cumbersome traction apparatus are not necessary in the care of the patient.

ALTERATION OF HORMONE BALANCE—In breast cancer and cancer of the prostate it becomes necessary to alter the patient's hormone balance in an effort to effect a change of the biologic characteristics of certain of these tumors. This is usually accomplished by the oral or parenteral administration of hormones. In addition however hormone balance can be altered surgically by castration in both sexes and on occasion this is augmented by the surgical removal of the ad

SPECIAL PROBLEMS

Many special problems arise in the treatment of far advanced malignant disease. Since the lives of many patients with malignant neoplasms can now be prolonged these problems arise with increasing frequency and require resolution. A few of them will be discussed here.

ANEMIA OF HYPERSPLENISM—With the development of chemotherapeutic techniques the hematologist is now able to prolong the lives of many of his patients suffering from the leukemias and lymphomas. In certain cases the destruction of the elements of the blood formed by the spleen becomes a major problem. Occasionally frequent transfusions become necessary to maintain the lives of patients in whom blood destruction is occurring at an ever increasing rate and with each transfusion the patient's reactions to the transfused blood become more acute. It is possible in selected cases to decrease the need for frequent transfusions and provide much relief of their symptoms by surgical removal of the spleen. To be sure these patients are poor surgical risks but the benefits to be obtained by splenectomy far outweigh the operative risk.

PATHOLOGIC FRACTURES—Surgical intervention is required when a pathologic fracture develops in a vertebral body and results in displacement of the vertebral alignment and compression of the spinal cord. This may be further complicated by dislocation of the fracture with compression of the spinal cord. A de

Radiation Therapy in the Relief of Pain in Malignant Disease

IN PROPERLY selected patients who are suffering pain as a result of advanced malignancy, the radiotherapist may offer relief in a manner that is often quite spectacular. Even when the pain is caused by metastases or direct extension from tumors which are ordinarily resistant to tolerable doses of radiation there may be complete relief if radiation is properly administered. The radiation therapist must be aware of the limitations and dangers of his modality. And rash promises to the patient must not be made nor should treatment be given where there is likelihood of doing more harm than good. Usually treatment cannot be given when the overlying skin is already severely damaged and the effects of prior treatment on sensitive tissues such as bowel and kidney, must be considered. The total body tolerance must also be remembered because when metastases are too numerous or the tumor bearing area too large, the amount of radiation that can be administered may be limited.

renal glands. These operative procedures are technically not difficult. The important factors are the selection of patients for these procedures and the preparation for surgery and postoperative maintenance therapy.

SUMMARY

Some of the surgical procedures available to the physician responsible for the care of the patient with advanced cancer have been discussed. Even when incurable, cancer is a chronic disease requiring as it develops increasing efforts on the part of the physician to allay fear, relieve pain and restore function. The general surgeon's role in the treatment of the patient with advanced cancer is related not so much to the relief of pain as to the restoration of function. Many situations that can be aided by general surgical procedures have not been covered, but from the discussion it is hoped that some general principles may be inferred to guide the physician in his approach to similar problems.

RADIATION COMBINED WITH CHEMOTHERAPY AND SURGERY

There are numerous reports in the literature concerning the combination of chemotherapy and radiation therapy. As yet there is no concrete evidence that there is more than an additive effect, but frequently there is good justification for the use of combined therapy. When substances such as nitrogen mustard or the folic acid antagonists are used, relief of pain may be slow or incomplete. In generalized disease the use of chemotherapy simultaneously with the application of radiation to the areas of most severe pain can produce more rapid and prolonged results.

Rarely, however, is radiation useful in combination with surgery. It is unfortunately true that radiation is difficult to give following surgery and that satisfactory doses cannot usually be administered. Time must elapse for adequate healing, recovery of the patient, etc. In most cases it is advisable to make a definite choice between the two modalities and use either one or the other. Surgery for advanced cancer is usually quite radical and its sequel is usually diminished blood supply and increased fibrous tissue. This situation prevents the use of adequate doses of radiation because of the danger of tissue breakdown. In addition, extensive surgery often requires the use of skin grafts which break down under the required dose of radiation.

Surgery designed as an implement of radiation is an entirely different matter. Actually the insertion of

to a dose which will accomplish relatively little

Many large volumes have been written on the role of radiation therapy in the management of malignancy. This chapter deals with only one small facet of the problem and will accordingly be strictly confined to the control of pain. The discussion of radium, radioactive isotopes and supervoltage radiation is brief because while these sources of radiation are most important in the general field they have but limited application in the control of pain. As a consequence the major emphasis is placed on the use of externally administered x rays in the ordinary range of voltage (200-250 kv) commonly but erroneously called "deep x ray therapy."

X rays in this range are available to most patients within the limits of continental United States and for the purpose to be discussed here will be found in the hands of a diplomate of the American Board of Radiology within a 50 mile radius of the referring physician. Modern transportation makes the daily trip for such treatment for the period of time usually required not too arduous. Adequate hospital facilities are usually available where the distance is too great or the patient is too ill to tolerate travel.

In general, the success of radiation therapy depends on the particular sensitivity of the malignancy to radiation. Lymphosarcoma, Hodgkin's disease, multiple myeloma and related reticuloendothelial diseases are very responsive to ionizing radiation. Chondrosarcoma, osteosarcoma and liposarcoma represent malignancies that are resistant to radiation.

volved tissues. Some otherwise well respected institutions advocate the use of relatively low voltage radiation in the range of 130–150 kv for rather deep seated lesions. Such treatment demonstrates ignorance of physical principles and it not only is without much value in providing pain relief but is often detrimental because excessive damage to the skin frequently prevents later attempts to produce palliation in the same area.

A wide range of radiation is now available. Low voltage x ray machines with beryllium window tubes can operate at such levels that the radiation hardly penetrates the skin. From this level the entire range is covered up to radiation produced by betatrons at 22 000 000 volts and by other instruments, such as synchrotrons, to much higher levels. The radiation from radium falls at about the 1 000 000 volt level but the application of radium and its by products is quite a different matter because containers may be inserted within body cavities or into diseased tissues to deliver the radiation directly without traversing normal tissues.

ARTIFICIAL RADIOACTIVITY

Since 1940 there has been a rapid development of a multitude of artificially produced radioactive elements. For various reasons only a few of these have proved practical in the treatment of disease. The three most important are radioactive phosphorus (P^{32}) radioactive iodine (I^{131}) and radioactive gold (Au^{198}).

sources of radiation into cavities or tissues is a surgical procedure and the preceding statements are not intended as a criticism of such technics

PREVENTION OF PAIN

Before mentioning specific instances and giving some treatment details prevention of pain should be considered. While in most cases extensions or metastases do not make themselves evident until they already produce pain there are occasions when experience will indicate that an inoperable and incurable malignancy is extending in such fashion that intractable pain will undoubtedly soon be present. In such cases judiciously given palliative radiation can be of great value. Radium, supervoltage radiation or ordinary x rays may be used depending on the nature and site of the lesion.

QUALITY OF RADIATION

The selection of the quality of radiation is the problem of the radiotherapist. Often there is a choice but in general the quality of radiation will depend on the depth of the lesion to be treated. Most pain producing lesions are deep seated and must be reached by radiation that is quite penetrating. It must be emphasized that the important thing is *the amount of radiation which acts on the tumor*. Radiation of the skin if not excessive is not important, nor is the dose to other organs or tissue but what is important, is to give the maximum possible dose needed while sparing unin-

Certain cases of ovarian malignancy with widespread peritoneal implants producing ascitic fluid are benefited by the use of colloidal radioactive gold. A solution of this substance, injected into the peritoneal cavity, spreads itself around fairly evenly and the results of the beta and gamma radiation often serve to decrease the production of ascites. This type of treatment is usually reserved for patients who do not have appreciable masses in the abdomen since most of the effect comes from the very slightly penetrating beta particles. Where masses are present treatment by external radiation is more successful.

Numerous malignancies produce pleural effusion and radioactive gold is useful in these conditions. Patients with effusion due to Hodgkin's disease, lymphosarcoma and other radiosensitive diseases show the best results as might be expected; less spectacular benefit is achieved in effusion due to metastatic cancer of the breast and similar malignancies. Results similar to those of radioactive gold are obtained by the use of colloidal chromic radioactive phosphate. There is little choice between the materials as regards effectiveness but from the standpoint of procurement, the rapid decay of radioactive gold is occasionally a disadvantage.

Recent experimental work has indicated that adrenalectomy may be supplemented by removal of the hypophysis. Because complete surgical ablation has been difficult and destruction by external radiation almost impossible, attempts have been made to eradicate the gland by implantation of radioactive sources.

Radioactive phosphorus has found its greatest usefulness in the treatment of the chronic leukemias and polycythemia vera. Because it is quickly accumulated in rapidly growing cells, the greater portion of a dose collects in the bone marrow. Here the beta particles or electrons, given off by the radioactive phosphorus as it decays, destroy the abnormal cells with a consequent beneficial effect on the disease process. It might be assumed from this that other rapidly growing abnormal tissues would be destroyed, but this is usually not so, because abnormal cell collections in locations other than the bone marrow find themselves in competition with the normal marrow for the radioactive phosphorus. The usual result is a seriously damaged bone marrow and but little effect on the tumor.

Radioactive iodine is rapidly collected in the thyroid gland, where its primary effect is achieved by beta emission, although it does produce some gamma radiation. It is used in the treatment of hyperthyroid disease, carcinoma of the thyroid, and more recently to produce myxedema in certain types of heart disease. In cancer of the thyroid, only certain types of tumors are affected—those whose structure resembles normal thyroid tissue and those giving some evidence of thyroid function. Even when thyroid tumors have metastasized, if iodine is concentrated by the metastases, benefit may be obtained. A few patients who had this condition and treatment are now living after more than five years without evidence of disease. No benefit can be expected, however, when little or no iodine is concentrated in the tumor.

involves the sacral plexus. In many patients with this type of disease, excellent relief of pain has resulted from a dose of as little as 2000 r to the tumor. Involvement of the brachial plexus by metastases of cancer of the breast or by upward extension of an apical lung tumor may frequently be very distressing. Symptoms from such involvement can often be relieved by the application of external radiation.

While pain is only occasionally a phenomenon in edema, grossly swollen limbs can be a serious burden and the tense swollen skin can sometimes be quite distressing. Local extension from carcinoma of the female generative organs often causes obstruction of the major pelvic veins and lymphatics, with resultant edema of one or both lower extremities. When prior radiation to the pelvis has not been carried to extremes, palliative measures may be carried out which will relieve these difficulties. Radiation should be directed to the involved areas with carefully measured doses to the tumor and recognition of possible damage to the bowel and skin. On the other hand, a frequent sequel of combined surgery and postoperative radiation for carcinoma of the breast is edema of the arm. This is most often caused by the scar tissue produced by both procedures, not by extension or dissemination of malignant processes. Further radiation therapy in such cases is contraindicated since it will only serve to increase the difficulty.

In similar fashion, palliative radiation therapy for pelvic tumors may relieve bowel obstruction. Often such treatment may be repeated even though the

Pellets of radio active yttrium (Y90) have been used for this purpose with some success Only time will allow full evaluation of this procedure

METASTATIC DISEASE AND LOCAL EXTENSION

Relief of pain caused by bone metastases is one of the most frequent requests made to a radiotherapist In general the results are good, in some instances, spectacular The results do not always depend on the radiosensitivity of the primary disease For example carcinoma of the breast is notably radioresistant, but properly administered x ray treatment will alleviate or even eliminate pain in many cases In the more sensitive tumors such as Hodgkin's disease and multiple myeloma relief can be even more striking but it must be pointed out that where pain is due solely to pressure on nerve roots by virtue of deformity little can be expected, for radiation cannot reconstitute for example, a totally compressed vertebral body At the other extreme painful metastases from hypernephroma give disappointing results However, no hard and fast rules can be made and an adequate trial of radiation of the proper quality to deliver a suitable dose to the tumor should be tried within the limits already mentioned

Not infrequently metastases or the local recurrence of a tumor involves nerve roots or nerve plexuses Here, again, surprising results are often seen even when the malignancy is known to be very radioresistant. Local recurrence of rectosigmoid carcinoma often

relief of obstruction may be very rapid when x ray is given to the mediastinum. The type of cell influences the degree of response, the best results occurring in the most anaplastic tumors.

RADIATION SICKNESS

The great wealth of literature on the management of radiation sickness and the multitude of measures suggested for its control testify to the lack of knowledge of its exact nature. In the absence of laboratory evidence of toxicity, a large portion of the condition must be considered psychogenic. Patients have been observed who became ill before their first treatment and others have been seen who underwent the same radiation and never experienced a moment's illness. Radiation is now so thoroughly publicized and talked about over the back fence that most patients will have an acquaintance who knows a neighbor or a friend who knows someone, who has "had those x ray treatments that make you sick at your stomach." Except in unusual cases, the ordinary treatment does not make the patient sick. Rarely is it necessary to suspend treatment because of nausea and vomiting, but even then the judgment of such suspension and the decision as to medication is best left to the radiation therapist.

Modern radiation therapy combines a knowledge of radiology and physics and, most of all, a wide experience in the art of the practice of medicine. Patients referred for radiation therapy are best left in the therapist's hands until the contemplated job is done.

malignancy is incurable. The huge spleen with painful tense capsule seen in some leukemias may shrink following x ray. Certain intracranial metastases particularly those from the sensitive tumors which produce headache, diplopia and many other symptoms may be promptly and often permanently relieved by radiation. In such cases adequate treatment will usually produce temporary loss of hair of which the patient should be warned. Before undertaking treatment that will cause a disfigurement such as this the entire situation should be evaluated in terms of the total life expectancy of the patient. No such treatment should be considered in patients who are near terminus due to other causes.

OTHER COMPLICATIONS

A major symptom of Hodgkin's disease is pruritus. Often this distressing condition will be present when no other evidence of the disease can be found. The condition can frequently be relieved by irradiation with 250 kv x ray to the epigastric lymph nodes. Since it is almost impossible to detect enlarged nodes in this area unless they are huge, it is not surprising that this treatment is efficacious in widespread Hodgkin's disease.

A frequent complication of inoperable carcinoma of the lung is compression of the superior vena cava with consequent dilatation of the vessels of the head and neck. While there is little evidence at present that radiation has curative possibilities in such tumors, the

CHAPTER 7

Psychological Aspects of Pain in Terminal Malignancies

ALL PEOPLE experience pain and all people experience death. Yet the emotional preparation for these experiences is as variable and various as the individuals who make up this world. Some people accept pain and death with equanimity. Others flee in terror.

Intractable pain associated with cancer places the greatest stress on the emotional or psychological defense mechanisms that can be experienced in the field of medicine. The management of pain in terminal malignancy may often be the greatest problem to the patient, the family, the hospital, and the medical personnel in attendance. There will be reciprocal stress in the patient, his family, and his doctor. In this situation the physician is called on to accept and demonstrate the extent of his personal ability and therapeutic skill. The reduction of pain depends on a constantly shifting relationship between the patient, the family, and the physician. An attempt to define the psychological factors which may be present for each of these three

Conflicting recommendations after a course of management has been agreed upon can only undermine the patient's confidence and the old adage of "too many cooks spoil the broth" is too frequently true when the referring physician tries to manage the problems of radiation therapy.

that of other sensations is accomplished by means of relatively simple and primitive neural systems which receive conduct and perceive impulses. It is on this aspect of pain that the most active therapeutic measures have been devised.

The reaction to pain on the other hand is a complex physiopsychological process which involves the highest cognitive or mental functions of the patient. It represents the emotional and psychological expressions resulting from the perception of pain. It is what the individual feels, thinks and does about the pain he receives. The pattern of reaction depends on what the sensation means to the individual in the light of his past life's experiences and his attitude toward it. His attitude in turn depends on the mood, emotional status, the will, the state of the various cerebral functional processes and the presence of anxiety and fear. The reaction pattern which usually, but not always immediately, follows on the perception of pain assumes the form of the classic "fight, flight or withdrawal."

Pain associated with cancer is not one of unvarying suffering but differs in quality, severity and duration depending on the mechanism producing it. Pain will fall into the classic divisions of superficial, deep and referred pain. Rarely is there pain of central origin or psychogenic pain.

Superficial or cutaneous pain is bright, prickling and exultating in character and nature. It can be accurately localized regardless of the site or origin. The duration varies, and this may cause the patient to interpret the pain as being of variable quality. Super

groups will be made here and suggestions for integration of the activities of all three groups will be given

Terminal and intractable pain occurs on the psychological background of these two factors (pain and death) which are most liable to produce disabling emotional patterns. It is a cornerstone of modern dynamic psychiatry that the activity of the mental apparatus is in general directed by the organism toward the attainment of pleasure the avoidance of pain and the preservation of the individual. All these are negated when the diagnosis of intractable pain resulting from a malignancy is known to the patient. It is remarkable that more attention has not been given to the methods of handling the emotional responses derived therefrom.

Because of the interlocking effect of pain and death on the psychological mechanisms of the individual it will be necessary in the following discussion to consider both of these facets and their interrelationship at all times. It will be necessary to consider the effect on the patient, and also the psychological attitudes of the family, the social environment and the doctor and other medical personnel who will be caring for the patient.

GENERAL CONSIDERATIONS OF PAIN

Certain concepts are necessary in order to understand and relieve pain. The basic factor involves two main processes: the perception of impulses giving rise to the sensation of pain and the reaction and response to this perception. The perception of pain like

of the individual, they are dependent on the intimate interrelationship between the perception of, and the reaction to pain

Intolerable or overwhelming pain is characterized by effects that are manifestations of what can be called an abnormal reaction to pain. The patient performs continuous purposeless movements, rolls about, struggles and frequently cries and yells. Observation or questioning reveals clouding of consciousness, and the patient's behavior is not influenced by his surroundings. Moreover the pain is very diffusely perceived and vaguely localized.

Severe pain is characterized by similar mental effects, only the patient is more aware of his surroundings. The pain is vaguely localized because of the mental effects which prevent the individual from focusing his attention to such localizations. The body is tensely fixed. The patient groans, winces and sighs during the height of the pain. Stimulation of the special senses—by loud noises or bright lights, for example—causes distress. Not infrequently the patient seeks sympathy, seclusion and inactivity in an attempt to minimize the pain—the withdrawal reaction.

Moderate pain is characterized by a fight or flight reaction which though momentary during the height of the pain, is so much in the foreground of total experience that primarily the pain is localized only roughly. Subsequently however with a special effort, exact localization is possible.

Mild pain is accurately localized and does not lead to any motor reaction. It does not impair conscious

facial pain may become an abnormal sensation usually taking the form of distressing cutaneous tenderness hyperalgesia, paresthesia and analgesia. There may also be sensations of itching, tickling and tingling.

Deep pain has a dull aching quality. It is extremely diffuse and poorly localized. It is usually accompanied by cutaneous tenderness, hyperalgesia and hyperesthesia located in parts remote from the stimulus. There is frequently muscular rigidity or contraction which is associated with gland and smooth muscle effects and deep tenderness. The localization and spread of deep pain depends on the intensity and duration of the stimulus. An increase in intensity makes the pain less localizable and more widespread. This pain may remain fairly localized to the involved organ or may be of a referred type.

Perhaps the greatest difficulty encountered by the clinician is the estimation of the intensity of pain that the patient is experiencing. This is because of the variability of individual reactions to pain making it difficult and at times hazardous to draw inferences regarding the intensity of such pain from observation of the patients.

In the following discussion on clinically observable mental and physical effects of pain it is to be emphasized that this division is an artificial one used for the sake of convenience and clarity.

MENTAL EFFECTS OF PAIN

The effects of pain depend on the severity, duration and quality and on the mentation, attitude and mood.

some cases as a result of sympathetic inhibition or parasympathetic stimulation there is a drop in blood pressure

RESPIRATORY SYSTEM—During severe pain the respiratory rate is, as a rule increased with a concomitant decrease in the volume, though it is not rare to observe an increase in the tidal exchange. If the pain involves the chest wall or the heart the result is splinting of the chest, and breathing is principally abdominal in character. If there is abdominal pain there is frequently a costal type of respiration.

DIGESTIVE SYSTEM—Severe pain is frequently accompanied by nausea and sometimes by vomiting. These effects are usually seen with a collapse type of pain reaction characterized by hypotension, weak pulse, sweating, pallor and mental confusion and are most frequently associated with overwhelming pain. In addition, severe pain frequently decreases or completely inhibits gastrointestinal functions, resulting in slowing of digestion and prolongation of the emptying time of the stomach.

GENITOURINARY SYSTEM—Prolonged pain of intense degree causes a diminution in the patient's renal function, apparently on a basis of vasoconstriction.

AUTONOMIC NERVOUS SYSTEM—Superficial sharp pain seems to cause a sympathetic hyperactivity manifested by pallor, *pulsus alternans*, tachycardia, sweating, goose flesh, dilatation of the pupils and rise in blood pressure.

All are manifestations of the fight or flight syndrome. Overwhelming deep pain causes a withdrawal reaction.

ness and it is experienced in the person's body but detached from the personality. This pain comes nearest to pure sensation. It involves only the perceptive phase of pain.

PHYSICAL EFFECTS OF PAIN

SYNCOPE—Aside from the mental effects already discussed there is one additional nervous system effect syncope which is primarily the result of overwhelming pain. There are often symptoms of collapse which may progress to syncope. This is probably secondary to sudden cerebral ischemia as the result of severe hypotension due to hyperactivity of the central nervous system.

CARDIOVASCULAR SYSTEM—The general effect on the cardiovascular system is stimulation with superficial pain and inhibition with deep pain.

Heart—Prolonged intense pain affects the heart and alters the T wave of the electrocardiograph. Pain and fear have a definite effect on the heart as evidenced by the many reported cases of sudden death of patients with heart disease during a painful experience.

Pulse rate—Pain alters the pulse rate. The type of change depends on the intensity of pain. Superficial pain causes a fight or flight reaction which is manifested by tachycardia and consequent increase in the pulse rate whereas severe deep pain causes a slowing of the pulse and may even cause cardiac arrest.

Blood pressure—Severe pain alters the blood pressure. It will frequently cause a rise in blood pressure in direct proportion to its intensity. Conversely in

a foregone conclusion of an inevitable progression to subsequent death. This chain of reasoning colors the patient's response to illness. The extremes of emotional behavior are frequently seen and require great skill and knowledge on the part of the physician.

The basic problem or factor in prolonged pain is the handling of fear. This fear may rise from conscious or unconscious sources. The conscious sources are fear of continuing pain or additional pain of mutilating surgery or other therapeutic procedures and of death. There also may be unconscious fears which become activated by the dependent state in which the patient is placed by his illness and by the symbolic significance of the various organs involved in terms of the patient's past emotional experience. There are also fears of separation from the family and of possible disintegration of the family unit and fears of economic chaos for the patient and for his family. The usual responses to fear are disturbances of affectivity, or the feeling life of the patient. These appear in proportion to the stability of the individual previous to the onset of his illness.

MENTAL REACTION PATTERNS

In any illness, some depression and anxiety commonly occur and so a reactive depression is an obvious outcome of a serious illness. Reactive depressions are those arising in response to obvious external causes which naturally might produce sadness. An autonomous depression may also occur. This type of

manifested by parasympathetic hyperactivity bradycardia drop in blood pressure, nausea vomiting sweating and alteration of gastrointestinal function

MUSCULOSKELETAL SYSTEM—Pain associated with deep somatic or visceral disease is accompanied by cutaneous tenderness hyperalgesia and hyperesthesia and muscular spasm Immobility causes skeletal muscle tension which may become a new source for noxious stimuli to aggravate the pain

METABOLISM—Pain is frequently accompanied by an increase in the metabolic rate and temperature of the individual This in turn increases the sensitivity to noxious stimuli and thus increases the severity of the pain Reflex irritability and oxygen demand are generally increased and in certain instances when pain is very severe these rise so greatly that a very large dose of opiate, or even a general anesthesia is required to lower them to normal

MENTAL OR PSYCHOLOGICAL FACTORS IN PAIN

The psychological effect of an illness on a patient is a function of the previously existing personality of the patient In general the more maladjusted the person was before the illness the more pathological will be his reaction to disease This is especially true in patients with malignancies With a malignancy there is a greater chance of pain suffering and fearful anticipation a greater chance of destruction or removal of organs and a greater chance of death A diagnosis of malignancy often carries with it in a patient's mind

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depression usually arises from unconscious guilt from interpersonal issues. Guilt results from unconscious ambivalence and hostility with resentful and aggressive impulses directed toward persons or the object of undesired obligation or toward persons on whom one is dependent for security. Hostile impulses originally directed toward other persons may become directed toward one's own self.

Anxiety is a condition of heightened and often disruptive tension accompanied by a vague but often most disquieting feeling of prospective harm and distress. Tension is a component of anxiety, but it is frequently recognized as a lesser form of anxiety, in that the patient has a continuing feeling of uneasiness, restlessness, dissatisfaction, dread and discomforting expectancy.

Fear is a response to an actual present danger. It does not persist when the external danger which gives rise to it is eliminated. Anxiety, on the other hand, with its persistent feeling of dread, apprehension and impending disaster, is a response to repressed dangerous impulses deep within the personality or to repressed feelings striving for consciousness. It differs from fear in being referable not to specific objects or events but to an irrational dread of situations that covertly symbolize unconscious conflicts and impulses. Anxiety and fear have much in common. Both are responses to and signals of danger.

The patient may also respond to fear by indifference or apathy, which would represent an excessive form of repression. Apathy could be regarded as a protective

form of defensive reaction perhaps against painful perception

Panic may occur as a response to fear. Panic is not merely a high degree of fear, but a fear based on prolonged tension with a sudden climax which is characterized by fright, extreme insecurity, suspiciousness, tendency to projection and disorganization. In this situation the symptoms of hallucinations and delusions of persecution are common. The patient may react with self assertion and aggressiveness and may manifest autonomic signs of great fear yet remain immobile because he does not dare to move.

All of these symptoms of mental disorder represent the patient's attempt in the face of great difficulty to maintain an existence in the best possible way.

REACTIONS TO ILLNESS

The meanings of a particular illness to a particular patient are based on conscious and unconscious sources. When the patient is given a diagnosis he has to absorb the information in terms of the knowledge he has of it and in terms of the knowledge the doctor gives him. The meaning of a diagnosis will therefore vary from patient to patient. For the average person the meaning of an illness is determined first of all by other cases which he considers to be of the same disease, whether really relevant or not. In addition the meaning of the illness may be distorted by ideas arising from early childhood experiences which have emotional connotations and were simultaneous with

feeling states which are irreconcilable to the patient at the present time

The normal reaction to illness implies some anxiety and some depression, which very soon decreases to a concern approximately commensurate with the organic illness. In other cases there may be an avoidance reaction in which the patient appears manifestly unperturbed, sometimes denying his illness and shows overactivity and false gaiety. This may be like a will o'-the-wisp and may turn into depression, anxiety or deliberate self harm by not following the physician's directions. Other patients may show a reactive depression with some prolonged emotional retardation and hypochondriasis. A more pathological response to illness would be a channeling of all previously existing anxiety into a new groove of concern. This may cause the patient to give up many of his diffuse neurotic disturbances and cause him to appear more tractable at the moment.

All severe incapacitating illnesses increase the need to be loved and cared for. Enforced inactivity, in turn adds to the wish to return to a dependent more or less childlike status. Such an unconscious desire may express itself in rationalizations, inappropriate symptoms and demandingness. Fears of possible harm by lack of care stand in the center of such behavior.

REACTIONS TO MALIGNANCY

In an illness due to a malignancy or suspected malignancy the gamut of emotion may run from the delu-

sion of having cancer to a complete denial of the disease by those already afflicted. All kinds of irrational attitudes come to the fore. These emotional attitudes are dependent on the patient's attitude toward danger and destruction; they represent his individual methods for handling his fears arising from conscious and unconscious sources. It is the meaning of "malignancy" or "cancer" which determines the emotional reaction. There may often be a magic attitude toward the diagnosis of cancer as if it were a death sentence, and this becomes the focal point of the psychodynamics of the patient.

Images that patients may have of malignancies range from those of having a body riddled with holes to an attribution of living invading "things," or an anthropomorphization of the invading cells.

There is, in all cases, a subjective meaning of the particular malignancy. To some people, for instance, an ulcer represents a hole in the body and this idea upsets them. Much of the emotional charge about this hole may be derived from infantile notions of the differences between boys and girls and the feeling that girls are different sexually because they have somehow been damaged. The concept of an ulcer as a hole then revives such early fears and derives much of its irrational horror from this source. On the other hand, some patients visualize their malignancies as growths. Even limited psychiatric investigation sometimes reveals that this growth inside the body is equated with another type of growth (a pregnancy). A little child cannot understand the facts of life and

unconsciously the ideas and fears of childhood live on to distort our grown up rational understanding. Such notions often add further terrors to the realism of malignancy.

Patients may conceive of themselves as being helpless and impotent against the cancer enemy. They feel like passive and helpless children. Doom stalks them in the form of worse imaginings. The emotional situation of the cancer patient has become more difficult because of a general artificial cancerphobia as the result of increased publicity about malignancies. Campaigns aiming to enlighten the public about malignant growths are often used by neurotically inclined individuals to increase their fear. Some people definitely do not want to know the truth about themselves. They look upon every examination for cancer as though they were already certain of a fatal verdict. It has been observed that once the diagnosis of cancer has been established the patient suddenly becomes much worse. The combination of the tumor plus the fear or the illusion that the diagnosis means a fatal verdict brings the patient to a state of melancholy and compulsive preoccupation with his symptoms, setting off a vicious cycle that brings him sooner to the end of his resistance. He may make life intolerable for himself and his family.

Because there is always a possibility that there may be relief, the dictum of treating anxiety whenever it is encountered and wherever it occurs should be adhered to. It is the task of the doctor to interpret such fears from some of the random remarks that the pa-

tient makes in order to cope with the realistic problem of the basic illness

REACTIONS TO IMMEDIATE DANGER OF LOSS OF LIFE

At the time of an actual immediate danger of loss of life there is frequently some alteration of brain function. Such changes often lower the level of consciousness and impair complex intellectual functions and this seems to facilitate a delay in the patient's recognition of the serious nature of his condition. The patient slowly comes to realize how sick he is. The changes in brain function seem to make it easier for him to restrict his awareness, to decrease pain perception and to perceive only those elements in the environment which he wants to perceive, and to delay recognition of the threat to life.

The defensive psychological reactions appearing in an attempt to handle the threat of death generally are of three types: (a) processes which tend to make the patient feel that his life is really not in danger; (b) processes in which the patient seems to feel that, even though his life is in imminent danger, it does not really matter—that he is not concerned by his impending death; and (c) processes which tend to make the patient feel that, even though his life is in danger now, it will not remain in danger—that there is something that can be done to correct this situation.

A given patient is not limited to any one of these defensive responses but may show different ones at different times. These responses may be aimed at com-

bating either the illness itself or the fear derived from the illness. They involve not only conscious thought and voluntary action but to a large extent automatic nonconscious processes.

The reaction of purposeful alteration is manifest in a denial of illness. The patient simply does not recognize that he is seriously ill although he is capable of recognizing many other equally complex facts of his environment. In addition, some patients reject not only recognition of the illness but most or all of their current and environmental situation as well. They appear to be largely out of contact with reality.

Another reaction is that in which the patient recognizes the nature of a current situation and concludes that he is going to die. This type of patient is frequently observed to be the seriously ill patient—tired, weak and in pain—who comes to feel that what happens to him does not really matter. At the moment it may seem to him that to die is only to rest quietly and escape from suffering. A similar instance of the acceptance and preparation for imminent death is that in which religious feelings play an important part. Here the individual in a time of emergency mobilizes powerful feelings of God's protection. While this is usually an emergency defense in that the patient feels that God will probably protect his life and let him avoid death, there is also the feeling that God will take care of him in case he should die. Thus he is prepared either way for whatever may happen.

Another type of reaction is that in which the patient feels that even though his life is in danger now, it

will not remain in danger. He seems to be in danger of being overwhelmed by emotionally painful stimuli and he handles the problem within himself by thinking about the situation only when he must do so and even then, allowing himself to have little or no feeling about it. He often seems indifferent, unemotional and apathetic.

Virtually all patients at some time or another clearly demonstrate the type of process in which a conscious effort is made to avoid thinking of an unpleasant experience.

These defensive reactions make it possible for the individual to avoid overwhelming disintegrative panic. Under optimal conditions they facilitate not only relief of fear but preservation of life and recovery from illness as well. In extreme forms, however, they may be biologically maladaptive since the individual sometimes abandons long range life preserving functions in favor of momentary relief from discomfort.

INDIVIDUAL REACTIONS TO PAIN AND REMOVAL OF ORGANS

As part of the therapeutic process for alleviation of chronic pain in malignancy various organs may be removed and reaction patterns may occur as a result of an injury to or destruction of a part of the body which has special or specific significance for the individual alone. The reactions will vary with the part of the body and the type of function affected. This is particularly true relative to areas of the body which

have a sexual connotation. For instance, breast cancer obviously afflicts an organ for which a woman bears much pride as an erotogenic zone and which is particularly invested with meaning from an emotional standpoint. Amputation of a breast may involve a total change of the patient's image of herself as a woman. It definitely alters her role as a sexual object to her husband and it alters her world somewhat.

Patients with a malignancy of the gastrointestinal tract are exposed to all the deprivations of diet that are current in the treatment of these diseases. And patients with anal difficulties have to face uncleanness, which may have been taboo ever since early childhood and which may deeply upset the individual.

The idea of a growth inside the body may revive irrational childhood fears of pregnancy (that is a form of internal growth) and notions of a bleeding opening in the body may again arouse primitive concepts of bodily mutilation.

Cancers of the larynx, ear, nose and throat are particularly invested with symbolic unconscious meaning derived from early childhood fantasies.

In pulmonary cancer, early anxiety may occur with a vague feeling of respiratory distress or embarrassment—as though breathing was not safe anymore.

Along with the cachexia that occurs as a part of illness, infantilism in the patient frequently appears. Hunger and fear of death break through the ordinary control of emotions.

Thus to each individual each part of the body has a different meaning and it is just this individualized

meaning that accounts for the different reactions to the various pains and procedures in the therapy of cancer

PATIENT-FAMILY REACTIONS

The chronic illness and persistent pain in terminal carcinoma may place strong and excessive stresses upon the family's emotional ties with the patient. The family members who have strong emotional attachments to start with are most likely to take the patient's fears, pains and fate personally. Panic often strikes them. Whatever guilt feelings they may have toward the patient emerge to plague them. They wish they had been pleasant and good to the patient and are now doubly struck by every injustice they feel they might have done. Hypochondriasis in members of the family of the one afflicted with a malignancy is often the result of unconscious thoughts such as "I have been so unkind to him that I too deserve to be fatally ill." An alert physician has to understand these feelings and other ramifications of the emotional identification of the family with the patient.

When the illness and pain are particularly prolonged, two reactions may occur in a family. Initially there is the strong identification with death, destruction and pain. Then as time passes, the identification may become so painful to the members of the family that they will erect psychologic defenses in order to protect themselves. The most common form of reaction is rejection of the need for prolonged identification with the patient. This takes the form of decreasing interest

and mild isolation of the patient, and visits to the patient may become briefer and less frequent. Despite the use of this device, however, the relatives may feel guilty because of actual or implied neglect, which will in turn generate feelings of hostility toward the sick relative. Such a reaction depends on the duration of the illness and the ability of the patient to communicate his anxiety, fears, and pain to the various members of the family.

If the patient is maintained at home, many frustrations and physical demands may be imposed on the family by the advanced illness. There may develop extreme weakness, incontinence, and bad odors. The pressure of caring for the individual under these circumstances is likely to arouse a resentment and, in turn, guilt feelings on the part of those who have to do the nursing.

The duration of the illness may also involve financial stress for the family. Chronic illness is expensive, and after the initial period of personal identification with the patient, the family may soon come to feel that a quick death would be of benefit to the patient and would indirectly relieve the financial strain imposed on the family. Within the family group there may be rivalry and conscious or unconscious competition for the patient's estate. While these matters are not discussed with the patient, they may be discussed at some length among the peripheral members of the patient's family group. These persons in turn may generate resentment and hostility because of the decrease of the estate by the prolonged illness. The frequent bed

side visitors may therefore be operating on a compassion made up of mixed motivations

There has been some tendency to keep the diagnosis of a malignancy a secret from the patient but to share it with a family member. This produces many difficulties. A daughter who has been told secretly that her mother suffers from cancer herself suffers a great deal of anxiety and probably communicates that fear and concern whether she wishes to or not. It is doubted that a policy of secrecy succeeds very often.

The doctor has the task of deciding what type of approach to use with the personality of each patient or relative in mind. In the vast majority of situations probably a rational discussion of impending problems with the patient and family will be most useful.

PATIENT PHYSICIAN REACTIONS

The fears and anxiety of the patient with carcinoma and pain will be influenced by the attitude or advice of his physician. Thoughtless and unfeeling statements may precipitate excessive fear and invalidism. Of necessity contact with any patient arouses feelings in the doctor just as the doctor arouses feelings in the patient. Working with a patient suffering from a malignancy causes special problems for the physician. First of all the patient with a malignancy is most likely to engender anxiety concerning death even in the doctor. And at the same time this type of patient constitutes a serious threat or frustration to medical ambition. As a result a doctor may react more emotionally and

less objectively than in any other area of medical practice. He may at times be carried away to make more optimistic statements than are warranted and at other times his deep concern may make him more pessimistic than is necessary.

As a result of the feeling of frustration in his wish to help, the doctor may have moments of annoyance with the patient. He may even feel almost inclined to want to avoid this type of patient.

As in all patient-physician contacts, the patient perceives the finest nuances of the doctor's attitude unconsciously if not consciously. The patient of course views himself as a sufferer and expects help from the doctor. His attitude is frequently like that of a child toward a parent. At the same time, the childhood attitudes which the patient ordinarily keeps under control but which appear more readily during a period of dependency and illness may lie behind his desires and demands on the physician and his attention. These unreasonable attitudes will need to be recognized by the physician. Also, to maintain a patient's relatively unneurotic attitude toward his illness, it is necessary that the doctor be aware of inappropriate emotions aroused in himself by the patient. Once the physician is aware of his own problems, he can exclude them or at least control them so as to cause minimal interference in handling the therapeutic program for the patient.

PATIENT CULTURE REACTIONS

Frequently cultural patterns dictate how the individual should bear pain. American culture emphasizes

independence and personal accomplishment. Excessive display of emotional reactions regardless of the cause, is frowned on. In addition there is a lack of sanctioned outlets for the satisfaction of passive dependent needs of the individual. The American family structure, in an early portion of the individual's life, has intense emotional relationships among all members. However since our culture emphasizes independent and personal accomplishment, the child's close attachment to the mother must be resolved. When the time comes for the individual to be separated from the family unit, latent deep seated dependent longings may emerge and the psychologic defense against this may precipitate an anxiety as these feelings come into the patient's awareness. Illness, pain and fear of death tend to activate the dependent longings. Conflict can easily arise since it may be very difficult for the individual to satisfy his need for these passive dependent needs and his previous concept of the necessity for a competitive constructive individuality. Our culture provides few defenses for this type of stress beyond a suppression of the need. If the individual's defenses break down he may feel angry toward himself and toward the members of his family. The patient must frequently admit death and pain as a part of nature beyond his control, but he can try to, or does, suppress his thoughts and emotions about these subjects. The demands of the social environment, excessive competitiveness, sexual repressions and contradictory codes bring individual frustrations and dilemmas and engender psychic conflicts. Social factors and

standards help to shape the adaptive effort of each individual but when operating with biological and psychological influences, may be partly responsible for the formation of personalities that eventually come to neurosis and psychosis

MODIFICATION OF THE PAIN REACTION PATTERN BY PSYCHOLOGICAL SUPPORT

In no other disease is the patient's need for moral or psychological support so great as in intractable pain associated with cancer. This assistance takes the form of not the usual psychotherapeutic procedure, but sincere sympathy understanding kindness and moral support by the physician. The aim of psychological support is to reduce tension fears and anxieties which produce hyperactivity of the mechanism for reception and reaction to pain. In such psychological support one begins at the base of the process which transforms "body" to "mind." This is essentially an investigation of psychosomatic relationships based on the personal social and cultural experiences of the individual and on the individual physiology and psychology.

To begin with the treatment of a patient will involve an investigation of his general life situation at the time the illness arose and of the sequence of events since that time. It is assumed, of course that a thorough history and physical examination have been made and that laboratory procedures have been completed as indicated, in order to establish the diagnosis.

The general physician is in a particularly advantageous position, since he may have known the patient for some time, may know his attitudes toward illness, pain and death and may have intimate knowledge of the family relationships.

It is perhaps easiest for the physician to proceed from physiological to psychological investigation and explanation to the patient. All too frequently, the patient has conscious fears which are exaggerated by obscure medical terminology and incomplete explanations. The simplest thing the physician can do is to clarify in simple terms the definition of the illness that has been diagnosed. This in turn will decrease the anxiety that always accompanies something which one does not understand. It may be necessary to institute a mild program of education regarding the physiology and anatomy of the body and the organs which are now affected. It is certainly wise to give a tentative explanation of the various therapeutic procedures which the patient may anticipate, the duration of the procedures and their purpose. Such explanation must be given in simple terms which the patient can understand or relate to his past experience. The rationale of the disease process and the healing phases which may occur should also be discussed. If pain is extreme, the physician may be more specific in telling the patient details of procedures to avoid increasing pain and in so doing he involves the patient in an active portion of the therapeutic program and allows him to share some of the responsibility in securing the desired results in treatment. A single explanation may

not suffice. Frequently the patient physician tolerance limit is approached by the patient's demands for repeated and detailed explanation. There is no point in showing impatience, irritability or annoyance at the time of these repeated demands. A simple way to avoid them is to ask the patient to define what he remembers of his own illness or to verbalize his illness in his own words. The physician should particularly avoid an attitude of despair or defeat. The patient is quick to sense this or a lack of interest and he may be forced into emotional patterns which defeat the eventual purpose of treatment. The physician should do all he can to give the patient a sense of confidence and security based on the conviction that everything will be done to relieve his suffering and that his problem is not meaningful to him alone.

The intimate relationship of the patient and physician makes it possible to explore many of the unconscious sources of fear and anxiety which the patient has. The patient frequently regards his doctor as a sort of confessor, friend, sympathetic and understanding listener and often a useful visitor. Particularly in respect to a malignancy in an organ which has a sexual connotation or pain arising from such a structure the doctor will need to inquire into the meaning of this condition to the patient. Such inquiry does not require extensive psychiatric knowledge but it is not unreasonable to assume that the physician will be aware, working wise, that destruction or removal of organs which are basic to the concept of masculinity or femininity will be emotionally traumatic. The ex

planation usually required of the physician should indicate a lack of change in the basic body image. If necessary, a discussion of childhood experience with various organ diseases can be undertaken. This can be done simply by asking the patient, "Whom have you known with illness of this type before?" or, "What do you remember about illnesses of this type?"

A patient with malignant disease who is suffering pain more or less constantly soon guesses the prognosis despite the efforts made to conceal his doom. He may ask questions concerning the possibility of death or may indicate that he expects death. If this subject is brought up by the patient, it should be met with understanding and consideration. A matter of fact explanation of the possibilities of death may be given together with reassurance that no matter how severe the illness there always is a possibility of arrest of pain and recovery. Depending on the experience of the physician and the patient's own religious attitudes the properly oriented priest, minister or rabbi may be used effectively in sharing the preparation for death. In general, a matter of fact sympathetic listening attitude is probably the best approach to this problem. Certainly there is little the physician can do to alter the fear of death.

An additional aid to the doctor may lie in the technique of handling the complaints regardless of how badly they are expressed. While "a stiff upper lip" approach may be used at times on the other hand it may be necessary to be permissive and to express a willingness to listen to the patient's bitterest complaints concern

ing his pain. Even a momentary description of the severity of the pain in whatever terms the patient has available may relieve sufficient tension so that he is able to carry on in a manner most suitable to his needs when persons other than his physician are present.

When the patient comes to realize the presence of malignancy and chronic pain, he may need to put his personal house in order. The physician can recommend that a business like review of the personal affairs of the patient be made in the same manner as if he were entirely well.

The family of the patient may also require a good deal of psychological support. The members of the family will certainly seek out the physician to express their uncertainties and fears concerning the patient. It will be necessary to answer questions of anatomy and physiology, but this should be done as briefly and simply as possible. This is probably most efficiently done by giving an explanation to a single stable individual who can then communicate with the other members of the family. Of course this procedure carries a risk of misinterpretation, but it is advantageous in that it lessens the time required to talk to each individual alone. One of the points that might be emphasized is that everything possible is being done for the patient. It is wise to avoid specific predictions as to the time of death or the duration of the illness. A physician who does state a specific time may be put in an extremely embarrassing position by a complete recovery.

In relation to visiting with the patient, the physician

can recommend that there be no exaggeration of interpersonal relationships with the patient. The patient is, after all, still a member of the family group and activities of the family will still be of interest and will aid the patient in avoiding a sense of separation and hopelessness in regard to his illness. It is equally important that an overconcern or overprotectiveness not be demonstrated by members of the family; the patient will read enough into their minimal changes in attitude without a questionable overconcern on their part. Other important factors are to assure accessibility to at least one responsible member of the family and to assure the family that they will be notified of any medical changes in the patient's condition. A responsible and stable member of the family may be encouraged to discuss the necessary reorganization of family relationships and personal and financial responsibility which will be necessary if and when the patient dies.

MODIFICATION OF THE PAIN REACTION PATTERN BY HYPNOSIS

As has been repeatedly emphasized so far in this chapter, there is a great emotional problem in each patient with cancer and with severe pain. If the emotional tension in the patient can be channeled away from a neurotic exaggeration of fear and self-pity to a more realistic and constructive point of view, this energy will be available to support the patient during therapy. When therapy is completed, the patient should have a more serene and confident attitude until death.

With such an approach there will be less pain less disturbance in bodily function and a reduction in the degree of dread that surrounds the subject of cancer

Hypnosis may be used to suppress symptoms or through application of analytical principles to express emotionally charged ideas In some patients hypnosis allows a control over the subconscious mind, and the mind can thereby be maneuvered to aid the cancer patient in his struggle for survival Hypnosis offers difficult problems and most of the responsibility rests on the physician who undertakes this type of therapy

Historically the physician has ample precedent for hypnosis since it probably is older than medicine It certainly was used in Egypt and Aesculapius was said to have been able to relieve pain by stroking his hands on the patient's brow The use of hypnosis has had repeated ups and downs and is now receiving new interest with a gradual diminution in both professional and popular resistance to hypnosis

Hypnosis may be defined as an artificially induced state characterized by heightened suggestibility In hypnosis a special integrative interaction of the organism with its environment results in certain sensory motor and memory changes The hypnotic situation is a special type of interpersonal relationship and phenomena observed in hypnosis are the result of the interaction between the hypnotist and the subject The behavior of the hypnotized individual represents a psychosomatic response to the cues of the operator within the framework of this relationship

At present there is no physiological or psychological theory available which accounts satisfactorily for all the phenomena encountered in hypnotic states. Also practically nothing is known concerning the reasons for the individual differences in hypnotizability or for the relationship of hypnosis to various related states such as barbiturate narcosis and drug intoxication. The actual hypnotic techniques should be learned under expert guidance. Such techniques are taught in most of the larger centers of psychological training and in many of the larger psychiatric hospitals. Hypnosis is a process which when learned will be of use in other areas besides the control of cancer pain.

In general, it has been noted that pain, anxiety and organ dysfunction in a patient with cancer can be influenced by hypnotherapy. The results are however proportional to the depth of the trance and the intensity of the program of therapy. Before the hypnotic process is begun it is essential that the hypnotist have a detailed history of the patient, with special attention to psychosomatic factors, previous impressions regarding hypnosis and the present social environment of the patient. It is certainly best that the subject of hypnosis be directly discussed with the patient and that the procedure be done with his permission.

In all circumstances the depth of hypnosis is the deciding factor in its success. For practical purposes there are three stages: a light, a medium and a deep trance. In a *light trance* the patient recognizes some influence but doubts that he was hypnotized. In a *medium trance* the patient is sure he was hypnotized.

but he can recall freely all the events that occurred. In a *deep trance* the subject realizes that he was hypnotized but his recall of the trance period is under the control to some extent of the hypnotologists suggestions. If after about three one hour periods of intensive work, a patient reaches only the light trance he cannot be helped by hypnosis. The patients who go into a medium trance can be helped, but the more severe the organic pain the more ephemeral will be the hypnotic control. Those who reach the deep or somnambulistic trance can be helped. Unfortunately such persons are rare constituting only 10-20 per cent of the population. Extensive disease, a distraught mind, pain and the fear of death make induction of hypnosis more difficult than in normal persons. Thus it seems that the most difficult thing to control under hypnosis is the very function that the physician most wants to affect.

The hypnotologist is an important factor in this problem, for hypnosis is a transference and a countertransference relationship just as is psychoanalysis. In hypnosis the interplay is not well understood by either party and is not well handled. Here the differences in sex, age, race and social situation of the patient and the hypnotologist become acutely important and may if these factors are diverse militate against success.

The main disadvantages of this form of therapy are the few good subjects, the large amount of time required and the necessity for an experienced and well trained hypnotologist to govern each case. The pos

sible deleterious effect on the health of the hypnotologist and the long period of time required for one patient, between onset of symptoms and death thus limits the number of patients a single therapist can manage. Then too public resistance to hypnosis persists.

The advantages of hypnotherapy for patients who enter a deep trance are numerous. Drug requirements are lessened, pain is relieved, organ dysfunction can be corrected as much as is possible, and depression, anxiety and fear are minimized. Life is prolonged and death is approached as is a night's sleep.

Prefrontal lobotomy interferes with the induction of the hypnotic state in proportion to the decreased ability of the patient to concentrate so that results appear to differ from the hypnotic state. *Narcohypnosis* helps to counteract superficial resistance but does not seem to aid otherwise in obtaining true hypnotic depth. It does not eliminate all resistance.

Efforts should be extended to learn what hypnosis is and how it alters physiological function. When these fundamentals are understood, its advantages will have a wider and more satisfactory application. Hypnotic experience has indicated that there may be a cancer personality. Intensive study shows that the patient with cancer is either an inhibited individual with repressed anger, hatred or jealousy or a good person consumed with self pity.

Hypnotism is not to be considered lightly. Its use must be restricted and it is safest in the hands of a competent psychiatrist who has had a particular in-

terest and experience in it. Other specialists and general physicians should use it only after adequate training and then only when other available methods are inadequate. The use of hypnotism can be compared to the performance of a difficult operation. Anyone can cut the skin, many can remove an appendix, but few should remove a stomach, a pancreas or a lung. The same is true of hypnosis. Anyone can learn to induce it, some can get therapeutic results, but only those with experience and training should attempt to cut out pieces of the mind.

CONCLUSION

The psychological problem of pain in terminal malignancy is a problem of the total relationship of the individual, the family, the physician and society. The attitudes which the patient has will be a product of past experience, both conscious and unconscious, the kind and degree of disease which he now has, the duration and severity of his pain and his personal attitude and preparations for death. The reaction to pain will be based on reducing the unknown. Attempts should be made to reduce fear and anxiety and to simplify personal, family and spiritual relationships. The ultimate substance of treatment should be that the physician is doing all he can to give the patient confidence and a sense of security based on the conviction that all is being done to relieve the suffering and that all of his needs will be met within the realm of reasonable possibility.

Index

A

- Abdomen malignancy
 - nerve blocks for 71 ff
 - complications 79 80 f
 - 82 f
 - neurosurgery for 108 f
 - referred pain in nerve
 - block for 78
 - spinothalamic chordotomy
 - for 96
 - wall involvement nerve
 - blocks for 78
- Abstinence syndrome *see* Addiction Drugs
- ACTH *see* Corticotropin
- Adanon *see* Methadone
- Addiction drug
 - see also* Drugs: addicting
 - Opiates Opioids Narcotic antagonists
 - abstinence symptoms from
 - narcotic antagonists 19
 - vs relief from pain 14
 - withdrawal syndrome 30
- Adenocarcinoma, 156
- Adrenal corticoids for
 - prostatic cancer 126

- Adrenalectomy
 - to alter hormone balance
 - 173 179 f
 - for female breast cancer
 - 120 ff
 - with castration 122
 - hormone therapy after
 - 121 f
 - for male breast cancer 123
 - for prostatic cancer 125 f
 - supplemented by radiation
 - hypophysectomy 187
- Adrenocorticotrophic hormone
 - see* Corticotropin
- Alcohol
 - see also* Ethyl alcohol Alcohol block
 - as nerve-necrotizing agent
 - 51 f
- Alcohol block
 - for head and neck 54 ff
 - intrathecal 40 ff 57 69
 - 81 82
 - vs chordotomy 105
 - local anesthetic used with
 - 50 66
 - for paravertebral sympathetic nerves 67 69

terest and experience in it. Other specialists and general physicians should use it only after adequate training and then only when other available methods are inadequate. The use of hypnotism can be compared to the performance of a difficult operation. Anyone can cut the skin, many can remove an appendix, but few should remove a stomach, a pancreas or a lung. The same is true of hypnosis. Anyone can learn to induce it, some can get therapeutic results, but only those with experience and training should attempt to cut out pieces of the mind.

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- Biliary tract (extrahepatic)
 malignancy surgery
 for 163 f
- Bladder malignancy
 ileal establishment of 165
 169 172
 nerve block for 78 80 81
 82
 surgery for 167 f
- Blood pressure during pain
 198 f
- Bone metastases
 in breast cancer x ray
 therapy for 176
 radiation therapy for 188
- Bowel obstruction by tumors
 radiation therapy for
 189
- Brain metastases radiation
 therapy for 190
- Breast, malignancy
 adrenalectomy for 120 ff
 with castration 222
 hormone therapy after
 121 f
 clinical management 114 ff
 corticoids for 128
 estrogen therapy 114 ff
 hypophysectomy for 106
 122 f
 contraindications 107
 incurable prognosis 148
 inoperable
 hormone treatment for
 176 179 f
 surgery for 175 ff
 x ray therapy for 176
- in male
 adrenalectomy for 123
 castration for 123
 estrogens for 123
 hypophysectomy for 123
 metastases
 humoral and chemical
 palliation for 114 f
 116 118 120
 x ray therapy for 188 189
 neurosurgery for 109
 oophorectomy for 120
 radiation castration for 120
- Bronchogenic cancer
 nerve block for 59 f
 surgery for 153
 treatments for 132
- Buccal mucosa malignancy
 nerve block for 54
- C
- Caffeine
 combined with codeine 21
 toxicity 15
 value in pain 15
- Cardiovascular system during
 pain 198
- Castration
 to alter hormone balance
 179
 for female breast cancer
 with adrenalectomy 122
 by irradiation 120
 for male breast cancer 123
 for prostatic cancer 124 f
 with androgens 126
 with estrogens 124 125
- Cecostomy 162
- Cecum malignancy surgery
 for 162
- Celiac plexus block *see*
 Splanchnic block
- Cervix malignancy
 estrogens for 127
 nerve block for 80 82

Alcohol block (cont)

- post alcohol neuritis 67 f, 83
- reactions to 83
- stellate ganglion 62 64
- subarachnoid 46
- for upper extremities 58

Alphaprodine

- and addiction 29
- administration and dosage 28 29
- for chronic pain 28 f
- pharmacology 28
- reactions to 29

Amethopterin *see* **Methotrexate****Aminopterin** pharmacology and dosage 137**Aminopyrine** toxicity 16**Ammonium sulfate** as nerve necrotizing agent 51 53**Amphetamine**

- in fear of pain 15
- value in pain 15

Ampulla of Vater malignancy surgery for 164**Amputation** nerve section for neuroma after 87**Analgetic intensity** 16

- maximum—determination of 17 f

Analgetics systemic 13 II

- see also* **Drugs and specific drugs**
- addicting 14 16 ff 18 20
- toxicity 18 II
- adjuncts 15 31 ff
- nonaddicting 14 15 f

Androgens

- complications from 136
- contraindications 136
- for female breast cancer complications from 118 ff
- dosage 119
- physiological actions 118 f
- of low androgenicity, 136
- after orchidectomy 126
- pharmacology and dosage 135 f

Anemia of hypersplenism 178**Antibiotics** use in nerve blocking 78**Antipyrine**

- toxicity 15 16
- value in pain 15

Anxiety, 202**Apathy**, 202 f**Arm**, *see* **Upper extremities****Ascites** prevention by Au¹⁹⁸, 187**Aspirin**

- toxicity 15
- value in pain 15

Aziguanine 145**Azaserine** 145**B****Barbiturates**

- as adjunct for severe pain 31
- in drug reaction therapy 85
- in fear of pain 15
- as premedicants for nerve block 84
- toxicity 15
- value in pain 15

- for chronic lymphocytic leukemia 130
- for Hodgkin's disease 129
- for hypercalcemia, 137
- for lymphosarcoma 129
- for multiple myeloma 132
- for skin cancer 133
- Corticotropin
 - for acute leukemia 131
 - contraindications 132
 - for bronchogenic cancer, 132
 - for chronic lymphocytic leukemia, 130
 - for Hodgkin's disease 129
 - for leukemias 127 130 131
 - for lymphomas 127 129 130
 - for multiple myeloma 132
 - pharmacology and dosage 133 f
 - for pulmonary cancer 127
 - with radiation therapy 133
 - for skin cancer 133
- Cortisone
 - for Hodgkin's disease 129
 - for hypercalcemia, 137
 - for leukemias 127
 - for lymphomas 127 129 130
 - pharmacology and dosage 134
 - for prostatic cancer 126
 - for pulmonary cancer 127
 - replacement, in adrenal ectomy 121 f
- Cranial nerve section 87 ff
 - see also Nerve root section
- Cross tolerance 17
- Culture patterns of patient and his reactions to illness 214 ff
- "Cures" for cancer, 113
- Cystostomy 174
- D
- Death
 - emotional response of patient to 193 f 200 ff 207 ff
 - from opiate intoxication 19
- Deltasone *see* Prednisone
- Deltra *see* Prednisone
- Demecolcin 145
- Demerol *see* Meperidine
- DEPA pharmacology 142
- Depression, reactive 201 ff
- Desoxycorticosterone with adrenalectomy 121 122
- Desoxyephedrine in drug reaction therapy, 85
- Desoxypyridoxine 145
- Diabetes insipidus after hypophysectomy 123
- Dicodid *see* Dihydrocodeinone
- Diethylene phosphoramidate *see* DEPA
- Diethylstilbestrol
 - complications from 136
 - for female breast cancer 116
 - complications from, 118
 - pharmacology and dosage 136
 - for prostatic cancer 125
- Digestive system
 - lower surgery for lesions of 160 ff

- Cervix malignancy (*cont*)
surgery for 170
- Cheek malignancy
neurosurgery for 88
- Chemical palliation 111 f
- Chemotherapy
for anemia of hypersplenism 178
for chronic lymphocytic leukemia 130
for Hodgkin's disease 128
with radiation 183
- Chest, malignancy
nerve block for 69 ff
complications 70
nerve root section for 90
- Chlorpromazine
administration and dosage 32
contraindications 32
with nitrogen mustard 141
with other drugs 32
pharmacology 32
premedicant for nerve block 84
reactions to 32
- Cholecystostomy 164 f
- Choledochostomy 166
- Chondrosarcoma radiation therapy for 182
- Chordotomy
cervical 96 97
vs intrathecal alcohol block 105
vs phenol nerve block 105
spinothalamic, 94 ff
complications from 95 f 97
- Cobra venom
as adjunct for severe pain 33
with opiates 33
pharmacology 33
reactions to 33
- Codeine
and addiction 20 f
administration 21
for chronic pain 14
compared with morphine 20 f
dosage 21
duration of action 21
maximum analgesic intensity of 18
with other drugs 21
pain threshold 20
patient reaction to pain 21
pharmacology 20 f
reactions to 21
toxicity 15 21
value in pain 15
- Colchicine chronic myelocytic leukemia, 130
- Colon malignancy surgery for 161 ff
- Colostomy 161 162 172
wet 161 172
- Committee on Cancer Diagnosis and Therapy of the National Research Council 113
- Common bile duct, malignancy surgery for 165 f
- Corticoids
see also Adrenal corticoids
Cortisone
for acute leukemia 131
contraindications 132
for breast cancer 128
for bronchogenic cancer 132

- dosage 116
- pharmacology 114 ff
- physiologic actions 117 f
- withdrawal bleeding 117
- for male breast cancer 123
- pharmacology and dosage 136 f
- for prostatic cancer 125
- with castration 124 125
- for solid tumors 127
- Ethinyl estradiol
 - for breast cancer 116
 - complications from 136
 - pharmacology and dosage 136
- Ethyl alcohol
 - see also* Alcohol
 - as nerve necrotizing agent 51 f
- Ethyl carbamate *see* Urethane
- Ethylene phosphoramidate derivatives pharmacology 142 f
- Extremities *see* Lower and Upper extremities
- Eye
 - malignancy nerve block for 53
 - ulceration from nerve blocking 53
- F
- Face malignancy
 - nerve block for 52 53 55
 - nerve root section for 90 f
 - neurosurgery for 88 110
- Family patient relationship 211 f
- Family physician relationship 193
- Fear
 - analgetic action of 37
 - definition 202
 - handling of 200 ff
 - of intolerable pain 14 f
- Feeding tube 157
- Folic acid antagonists
 - for acute leukemia 131
 - antidote for 138
 - complications from 137 f
 - for lymphosarcoma 129
 - misnamed 138
 - pharmacology and dosage 137 f
- Folinic acid: antidote to folic acid antagonists 138
- Foot *see* Lower extremities
- Forehead malignancy neurosurgery for 88
- Fowler's solution
 - for chronic myelocytic leukemia 130
 - pharmacology 138
- Fractures pathologic
 - due to tumor growth 35 f
 - surgery for, 178 f
 - in metastases from breast cancer 176
 - x ray therapy for 176
 - of spine
 - surgery for 178 f
 - x ray therapy for 176
- G
- Gallbladder malignancy: surgery for 164
- Gastroenterostomy 158 f
- Gastrojejunostomy 159
- Gastrostomy 153

- Digestive system (cont)**
 during pain 199
 upper surgery for lesions of 156 ff
- Dihydrocodeinone** pharmacology and dose 22
- Dihydromorphinone**
 and addiction 24
 dosage 24
 euphoria from 25
 maximum analgetic intensity of 18
 pharmacology 22 24 f
 reactions to 25
- Dilaudid** *see* Dihydromorphinone
- one 4 Dimethanesulfonyl butane *see* Myleran
- Diodrast** for x ray guidance in nerve blocks 38 f 52 62 64 65 67 74 76 80
 reaction to 87 74
- Dipropionate** for female breast cancer 116
- Dolophine** *see* Methadone
- Drugs**
 see also Analgetics Opiates Opioids Narcotic antagonists and specific drugs
 addicting 14 16 ff 20
 maximum analgetic intensity—determination of 17 f
 tolerance—method of estimation of 16 f
 combined, to avoid respiratory depression 19 f
 depressant 19 f
 excitatory 19
 for nerve blocks *see* Nerve blocks
 nonaddicting 14 15 f
 rotation of 19
 toxicity signs of 15 16 18 ff
 withdrawal syndrome 30
- Duodenum** malignancy
 nerve block for 77
- Dysphagia** relief for 156 ff
-
- Ear** malignancy root section for 92 93
- Edema** from malignancies radiation therapy for 189
- Effusions** pleural Au¹⁹⁸ for 187
- Endometrium** malignancy surgery for 172
- Esophagus** malignancy
 nerve block for 57 59
 radiation therapy for 157
 surgery for 153 156 f
- Estradiol** for breast cancer 116
- Estrogen** therapy
 see also Estrogens
 for breast malignancy 114 ff
 general considerations 111 ff
 with radiation therapy 116
- Estrogens**
 see also Estrogen therapy
 complications from 136
 for breast cancer
 complications from 116 117 f

- Iodine radioactive, 185 186
Iodopyracet, *see* Diodrast
Isompecaine *see* Meperidine
Isotopes radioactive 185 ff
see also specific agents and
conditions

J

- Jaundice obstructive surgery
for 163 ff
Jaw malignancy nerve block
for 55 57

K

- Kidney
see also Urinary tract
failure 149
malignancy surgery for
167

L

- Laminectomy 178
Larynx malignancy
see also Respiratory tract
nerve block for 57
surgery for 152 ff 151
Leg *see* Lower extremities
Leg bag 174
Leukemia
acute-treatment, 130 ff
chemotherapy for 178
chronic
lymphocytic-treatments
130
myelocytic-treatment 130
P32 for 186
Leukotomy
bifrontal and abstinence
syndrome 30

- frontal 101 ff
complications from 102
104

Levallorphan

- with levorphan for chronic
pain 20
for severe opiate-induced
respiratory depression
19
and withdrawal syndrome
30

Levo dromoran *see* Levorphan

Levorphan

- and addiction 29
administration and dosage
29
for chronic pain severe 20
with levallorphan for
chronic pain 20
maximum analgetic inten-
sity of 18
pharmacology 29
reactions to 29

Life expectancy vs addiction
13 fLip malignancy neurosur-
gery for 88Liposarcoma radiation
therapy for 182

Liver malignancy

- nerve block for 77
neurosurgery for 108 f
surgery for 163 ff

Lobotomy *see* Leukotomy
frontalLocal extensions of tumors
radiation therapy for
188 ff

Genital system

female surgery for lesions
of 170 ff

male surgery for lesions of
173 ff

Genitourinary system during
pain 189

Gold radioactive 185 187

G T 41 *see* Myleran

H

Harrison Narcotic Act 20

Head malignancy

nerve blocks for 52 ff 62

pain after irradiation of 58

Heart during pain 198

Heart disease Au¹⁹⁹ for 186

Hodgkin's disease

effusion due to Au¹⁹⁹ for
187

radiation therapy for 182
188

for pruritus of 190

treatments 128 f

Hormone therapy

general considerations 111
ff

for inoperable cancer of the
breast, 176 179 f

for prostatic cancer 173
179 f

Humoral palliation 111 ff

Hycodan *see* Dihydrocode-
none

Hydrocortisone

with adrenalectomy 121

pharmacology and dosage
134

Hydronephrosis

with pyelonephritis 149

surgery for 168 169 170

3 Hydroxy N methylmor-

phinan tartrate *see*
Levorphan

Hymorphan *see* Dihydromor-
phinone

Hypercalcemia treatment
137

Hypernephroma metastases
from radiation therapy
for 188

Hyperthyroid disease I¹³¹
for 186

Hypnosis

drugs used for 31

for pain 221 ff

Hypopharynx, malignancy

radiation therapy for 157

surgery for 154 156 f

Hypophysectomy 106 f

see also Hypophysis
complications from 106
107

for female breast cancer
122 f

complications from 123

for male breast cancer 123

for prostatic cancer 126

by radiation 187 f

for prostatic cancer 126

Hypersplenism anemia of
treatment for 178

I

Illness patient reaction to
203 f

Intestines

obstruction surgery for
160 ff

small nerve block for
malignancy of 77

- Methadone**
and addiction 27
administration and dosage 27
for chronic pain 27
pharmacology 27
reactions to 27
toxicity 27
- Methotrexate** pharmacology and dosage 137
- Methoxamine** with adrenal ectomy 121
- 6-Methyldihydromorphinone** pharmacology and dosage 25
- Methyltestosterone** pharmacology and dosage 135
- Methypylon** as adjunct for severe pain 31
- Meticorten** *see* Prednisone
- Metopon** *see* 6-Methyldihydromorphinone
- Moral support** 216 ff
- Morphine**
see also Opiates Opioids
addiction 24
administration of 22
analgesic effect, 22 ff
contraindications 24
dosage 22
euphoria, 23 f
maximum analgesic intensity of 18
patient reaction to pain 23 f
reactions to 23 24
- Mouth malignancy** nerve block for 52 54 f 56 f 57
- Musculoskeletal system**
during pain 200
- Mustargen** *see* Nitrogen mustard
- Mycosis fungoides** treatment 132
radiation therapy 182 188
- Myeloma multiple** treatment 132
- Myleran**
for acute leukemia 131
for chronic myelocytic leukemia, 130
complications from 139
pharmacology 139
- N**
- Naja** *see* Cobra venom
- Nalline** *see* Nalorphine
- Nalorphine**
for severe opiate induced respiratory depression 19
and withdrawal syndrome 30
- Narcotic antagonists**
and addiction 19
with opiates to avoid respiratory depression 19 f
and withdrawal syndrome 30
- National Research Council**
Committee on Cancer
Diagnosis and
Therapy 113
- Neck malignancy**
nerve blocks for 52 ff 58 62
neurosurgery for 109 f

- Lower extremities
 edema from pelvic malignancies radiation therapy for 189
 malignancy
 nerve blocks for 81 ff
 —complications from 82 f
 surgery for 177
 pain after amputation
 nerve section for neuroma 87
- Lungs malignancies
 and dilatation of blood vessels of head and neck
 —radiation therapy for 190
 metastases from radiation therapy for 189
 nerve blocks for 58
 complications from 58
 neurosurgery for 109
 spinothalamic chordotomy for 96
- Lymph nodes iliac malignancy surgery for 171
- Lymphoblastomas treatment 133
- Lymphomas
 chemotherapy for 178
 surgery for 153
- Lymphosarcoma
 effusions due to—Au¹⁹⁸ for 187
 radiation therapy for 129 182
 treatment 129 f
- M
- Mastectomy radical pain from nerve block for 71
- Mechlorethamine *see* Nitrogen mustard
- Mediastinal lymph malignancy
 surgery for 153
- Melanocarcinoma incurable prognosis 148
- Mental reaction patterns 201 ff
- Meperidine
 contraindications to 27
 dosage 26
 maximum analgetic intensity of 18
 pharmacology 26
 reactions to 26 f
- 6 Mercaptopurine
 for acute leukemia 131
 for chronic myelocytic leukemia 130
 complications from 144
 pharmacology and dosage 143 f
- Mesentery malignancy nerve block for 77
- Metabolism during pain 200
- Metastases
 of breast cancer
 to bone hormone therapy of 176 179 f
 humoral and chemical palliation 114 f 116 118 120
 radiotherapy for 188
 intracranial radiation therapy for 190
 I¹³¹ for 186
 of prostatic cancer 123 f
 radiotherapy for 188 ff

- metastatic involvement of
 - radiation therapy for 188 189
 - sacral, radiation therapy for 189
 - sciatic
 - neurosurgery for 172
 - surgery for pain 149 170 f 172
 - Nerve root section, 89 f
 - complications from 91 f
 - Nerve roots metastatic in
 - involvement of radiation therapy for 188
 - Nervous system autonomic during pain 199 f
 - Neuromas resection of 87
 - Neurosurgery
 - see also* specific procedures
 - consideration of 86
 - in face 110
 - in neck, 109 f
 - in pelvic cavity 79 108
 - stereotaxic lesions 100 f
 - in thorax, 69 109
 - in throat, 110
 - in upper abdomen 108 f
 - Nisentil, *see* Alphaprodine
 - Nitrogen mustard
 - for acute leukemia, 131
 - for bronchogenic cancer 132
 - chlorpromazine with 32
 - for chronic leukemias 130
 - complications from 140
 - for Hodgkin's disease 128
 - for lymphosarcoma 129 130
 - pharmacology and dosage 140 f
 - relation to radiation therapy, 140
 - for skin cancer 133
 - Noludar as adjunct for severe pain 31
 - Norepinephrine in drug reaction therapy, 85
 - Nose malignancy
 - nerve block for 52
 - neurosurgery for, 88
 - Nu 1196 *see* Alphaprodine
- O
- Oophorectomy for breast cancer, 120
 - Opiates
 - see also* specific agents
 - with antagonists to avoid respiratory depression 19 f
 - with chlorpromazine 32
 - for chronic pain, 14
 - with cobra venom 33
 - death from, 19
 - depressant effects 19 f 31
 - dosages of compared with morphine 20
 - excitatory effect, 19
 - and narcotic antagonists 19
 - withdrawal syndrome 30
 - Opioids
 - see also* Opiates and specific agents
 - for chronic pain 14
 - dosages of compared with morphine 20
 - and narcotic antagonists 19
 - withdrawal syndrome 30
 - OPSPA
 - complications from 145
 - pharmacology 144 f

Neoplasms

extent and surgery 149 f

type of disability and surgery 150

types of and surgery 147 f

Neo synephrine in drug

reaction therapy 85

Nerve blocks

for abdomen 71 ff

complications from 79

80 f 82 f

alcohol *see* Alcohol block

celiac plexus *see* Nerve

block splanchnic

for chest 69 ff

complications from 70

drugs for

antibiotics with 78

local anesthetics 49 f 66

—reactions to 84 f

nerve-necrotizing agents

51 f

phenol 62 63 64 67 74

f 80

—reaction to 67

pontocaine 45 68

premedication for 84

procaine 68

tetracaine 56

epidural 46 f 71

for head 52 ff 62

eye complications from

53

under x ray guidance 54

55

intercostal 69 ff

intrathecal 39 ff

for lower extremities 81 ff

complications from 82 f

lumbar paravertebral sym-

pathetic 79 ff

complications from 80 f

after mastectomy (radical)

71

for neck 52 ff 62

under x ray guidance 54

55

paravertebral sympathetic

66 ff

complications from 67 ff

under x ray guidance, 65

67 76 80

patience in 35 39

for pelvic cavity 78 ff

complications from 79

80 f

peripheral 47 f

for pleura 69

principles of 34 ff

splanchnic 71 ff

under x ray guidance 74

75

stellate ganglion block 60

ff

complications from 62 ff

77 f

under x ray guidance 62

63 64

sympathetic 48 f

technics 34 f 36 f 39 ff

for thoracic viscera 66 f

after thoracotomy 69

for thorax 59 ff

for upper extremities 58 62

complications from 58

under x ray guidance 38 f

52

Nerve necrotizing agents 51 f

Nerve plexuses

brachial radiation therapy

for 189

- Panic 203
 Paraminophenols
 habit forming, 10
 toxicity of 15, 16
 value of in pain 15
 Paranasal sinuses malignancy
 nerve block for 52
 53 f 55
 Parathyroids malignancy
 surgery for 154
 Patient
 attitude of, and surgery
 151 f
 culture patterns of and re
 actions 214 ff
 family relationship 211 ff
 general physical status of
 and surgery, 150 f
 physician relationship 193
 213 f 217 ff
 reaction of
 to illness 203 f
 to immediate danger of
 death 193 f 200 ff
 207 ff
 to malignancy 204 ff
 to pain 200 ff
 to removal of organs
 209 ff
 Pelvic bones malignancy
 nerve block for 82
 Pelvic cavity malignancy
 nerve blocks for 78 ff
 complications from 79
 80 f
 neurosurgery for 79 108
 complications from 108
 Pelvic exenteration 171
 Penis malignancy surgery
 for 174 f
 Pethidine *see* Meperidine
 Phantom limb pain, 82
 Pharynx malignancy spino
 thalamic tractotomy
 for 99 f
 Phenacetin
 habit forming 16
 toxicity of 15
 value in pain 15
 Phenergan premedicant for
 nerve blocking 84
 Phenol
 in nerve blocking 62, 63
 64 67 74 f 80
 reaction to 67 74 f
 vs chordotomy, 105
 as nerve-necrotizing agent
 51 f
 Phenothiazine premedicant
 for nerve blocking 84
 Phosphate radioactive 187
 Phosphorus radioactive 185
 186
 Physician
 moral obligations of 152
 patient relationship 193
 211 f 217 ff
 relationship with patient's
 family 193
 Pitressin *see* Vasopressin
 Pleura malignancy nerve
 block for 69
 Pleural effusion Au¹⁹⁸ for
 187
 Polycythemia vera P³² for
 186
 Pontocaine in nerve blocking
 45 68
 Potassium arsenite solution
 see Fowler's solution
 Prednisone
 for acute leukemia 132

Oropharynx malignancies of
surgery for, 157 f

Osteosarcoma radiation ther-
apy for 182

Ovary malignancies

Au¹⁹⁸ for 187

radiation therapy for 172 f

surgery for 172

Oxapentamethylenediethylene
thiophosphoramide
see OPSPA

P

Pain

see also Patient

blood pressure during 198
f

in cancer 195

cardiovascular system dur-
ing 198

cutaneous 195 f

deep 198

degree of and prognosis
13 14

digestive system during 199

emotional response of patient
to 193 f 200 ff 209
ff

fear with handling of 200
ff

general considerations 194
ff

genitourinary system dur-
ing 199

heart action during 198

and hypnosis 221 ff

intolerable 14 f 197

intractable patient's re-
action to 193 f

mechanisms of 34, 35 f

mental effects of 198 ff
200 f

metabolism during 200

mild 197 f

moderate 197

modification by psychologi-
cal support 216 ff

moral support in 216 ff

musculoskeletal system dur-
ing 200

nervous system during 199
f

pathways anatomy of 34
36

perception of 194 f

phantom limb 82

physical effects of 198 ff

physiopsychological process
of 195

prevention by radiation 184

psychological aspects 193
ff 200 f

psychological support in
216 ff

pulse rate during 198

referred abdominal nerve
blocks for 78

respiratory system during
199

severe 197

superficial 195

syncope during 198

terminal—patient's reaction
to 193 f

Pancreas malignancy

nerve block for 77

neurosurgery for 108 f

surgery for 163 f 165

sympathectomy for 105

Pancreaticoduodenectomy

164

S

- Salicylates
 - with codeine 21
 - toxicity of 15
 - value in pain 15
- Salivary glands malignancy
 - nerve block for 54
- Scalp malignancy neurosurgery for 88
- Sedatives as adjunct for severe pain 31 32
- Sinuses paranasal malignancy nerve block for 52 53 f 55
- Skin malignancy
 - nerve block for 52
 - treatment, 132 f
- Spine malignancy
 - in cord laminectomy for 107
 - intrathecal alcohol injection for 69
 - pathologic fractures
 - surgery for 178 f
 - x ray therapy for 176
- Spleen
 - enlarged in leukemia radiation therapy for 190
 - hypersplenism anemia of chemotherapy for 178
 - surgery for 178
- Splenectomy 178
- Stereotaxic lesions 100 f
 - complications from 101
- Stilbamidine for multiple myeloma 132
- Stilbestrol *see* Diethylstilbestrol
- Stomach malignancy
 - nerve block for 77
 - neurosurgery for 108 f
 - surgery for 156 ff
- Submaxillary glands malignancy nerve block for 57
- Surgeon role in treatment for cancer 186
- Surgery
 - general considerations before
 - attitude of patient 151 f
 - extent of lesion 149 f
 - physical status of patient 150 f
 - type of disability 150
 - type of neoplasm 147 f
 - procedures to control pain 146 ff
 - psychological reactions to removal of specific organs 209 ff
 - with radiation 183 f
 - special problems 178 ff
- Sympathectomy 105 f
- Sympathomimetics
 - toxicity of 15
 - value of in pain 15
- Syncope during pain 198

T

TEM

- for acute leukemia 131
- for bronchogenic cancer 132
- for chronic leukemias 130
- for Hodgkin's disease 128
- for lymphosarcoma, 129 130
- pharmacology and dosage 142
- for skin cancer 133

- Prednisone (*cont*)
 pharmacology and dosage 134 f
 complications from 135
 Premarin for breast cancer 116
 Prisilidene *see* Alphaprodine
 Procaine in nerve blocking 68
 Prostate malignancy
 adrenal corticoids for 126
 adrenalectomy for 125 f
 androgens after orchidec-
 tomy 126
 castration for 124 f
 clinical management 123 ff
 estrogens for 125
 hormone treatment for 173
 179 f
 hypophysectomy for 126
 metastasis in 123 f
 nerve block for 78 80 82
 surgery for 173 f
 Y⁹⁰ for 126
 Pruritus of Hodgkin's disease
 radiation therapy for 190
 Psychological support and re-
 action to pain 216 ff
 Pulse rate during pain 198
 Purinethol, *see* 6 Mercapto-
 purine
 Pyelonephritis
 hydronephrosis with 149
 surgery for 168 169 170
 Pyrazolones
 toxicity 15 16
 value in pain 15
- II
- Radiation sickness 191 f
 corticotropin for 133
 Radiation therapy 181 ff
 with chemotherapy 183
 chlorpromazine with 32
 contraindications 181
 with estrogens 118
 isotopes radioactive 185 ff
 for local extensions of
 malignancies 188 ff
 for metastatic disease 188 ff
 and nitrogen mustard 140
 for pain prevention 184
 quality of radiation 184 f
 radiation sickness 191 f
 with surgery 183 f
 after urinary diversion 169
 voltage 184 f
 Radon seed implantation in
 head pain following 56
 Rectosigmoid malignancy
 see also Rectum
 local recurrence—radiation
 therapy for 188 f
 nerve block for 78 82
 Rectum, malignancy
 nerve block for 80 81
 surgery for 150 f 161
 Religion in terminal illness 208 219
 Respiratory depression from
 opiates 19 f 31
 Respiratory system during
 pain 199
 Respiratory tract malignan-
 cies surgery for 152
 ff
 Reticuloendothelial system
 diseases radiation therapy
 for 182
 malignancies surgery for
 152 ff

S

- Salicylates
 - with codeine 21
 - toxicity of 15
 - value in pain 15
- Salivary glands malignancy
 - nerve block for 54
- Scalp malignancy neurosurgery for 88
- Sedatives as adjunct for
 - severe pain 31 32
- Sinuses paranasal malignancy nerve block for
 - 52 53 f 55
- Skin malignancy
 - nerve block for, 52
 - treatment, 132 f
- Spine malignancy
 - in cord laminectomy for 107
 - intrathecal alcohol injection for 69
 - pathologic fractures
 - surgery for 178 f
 - x ray therapy for 176
- Spleen
 - enlarged in leukemia radiation therapy for 190
 - hypersplenism anemia of chemotherapy for 178
 - surgery for 178
- Splenectomy 178
- Stereotaxic lesions 100 f
 - complications from 101
- Stilbamidine for multiple myeloma 132
- Stilbestrol *see* Diethylstilbestrol
- Stomach malignancy
 - nerve block for 77
 - neurosurgery for 108 f
 - surgery for 156 ff
- Submaxillary glands malignancy nerve block for 57
- Surgeon role in treatment for cancer 186
- Surgery
 - general considerations before
 - attitude of patient 151 f
 - extent of lesion 149 f
 - physical status of patient 150 f
 - type of disability 150
 - type of neoplasm 147 f
 - procedures to control pain 146 ff
 - psychological reactions to removal of specific organs 209 ff
 - with radiation 183 f
 - special problems 178 ff
- Sympathectomy 105 f
- Sympathomimetics
 - toxicity of 15
 - value of in pain 15
- Syncope during pain 198

T

TEM

- for acute leukemia 131
- for bronchogenic cancer 132
- for chronic leukemias 130
- for Hodgkin's disease 128
- for lymphosarcoma, 129 130
- pharmacology and dosage 142
- for skin cancer 133

TEPA

- for chronic leukemia 130
- for Hodgkin's disease 128
- pharmacology 142

Testicles malignancy surgery

for 173

Testosterone

- complications from 136
- for female breast cancer 119
- pharmacology and dosage 135
- for solid tumors 127

Tetracaine *see* Pontocaine**6 Thioguanine** 145**ThioTEPA**

- for chronic leukemias 130
- complications from 143
- pharmacology and dosage 142 f

Thoracotomy nerve block for pain after 69**Thorax malignancy**

- see also* Respiratory tract
- nerve blocks for 59 ff 66 f
- neurosurgery for 69 109
- spinothalamic chordotomy 94 ff

surgery for 152 ff

Thorazine *see* Chlorpromazine**Throat malignancy**

- nerve block for 52
- neurosurgery for 110
- root section for 92 f

Thyroid gland

- function in I^{131} therapy 186

malignancy

- I^{131} therapy for 186
- nerve block for 57

surgery for 154

Tic douloureux nerve root

section for 91

Tolerance

- cross tolerance of drugs 17
- in drug addiction method of estimation of 16 f

Tongue malignancy

- nerve block for 54 f 56 f
- surgery for 154

Tracheobronchial tree malignancy

- nerve block for 59 f
- surgery for 152 ff

Tracheotomy 154 ff**Tractotomy spinothalamic**

97 ff

- complications from 97 ff

Triethylene amine *see* TEM**Triethylene phosphoramidate**

see TEPA

Triethylene thiophosphoramidate *see* ThioTEPA**Tumors**

- large ulcerated bleeding—surgery for lesions of 175 ff
- local extensions of—radiation therapy for 188 ff

U**Upper extremities**

- edema after treatment for breast carcinoma 189
- malignancy
 - nerve blocks for 58
 - complications from 58 62
 - surgery for 177
- pain after amputation—nerve section for 87

Uremia, 149 170 172

Ureterostomy 168

Ureters malignancy surgery
for 168 f 170

Urethane

for acute leukemia 131

for chronic leukemia, 130

complications from 141

for multiple myeloma, 132

pharmacology and dosage
141

Urinary diversion 168 ff 172

with radiation therapy 169

Urinary incontinence 170 174

Urinary tract

see also kidney

surgery for lesions of 167 ff

Uterus malignancy, nerve
block for 78 82

V

Vasopressin replacement

after hypophysectomy
123

Vasoxyl, see Methoxamine

Veins iliac malignancy sur-
gery for 171

Vulva malignancy surgery
for 173 177

W

Withdrawal syndrome see
Addiction

X

X ray therapy see Radiation
therapy

Y

Yttrium radioactive
for hypophysectomy 188
for prostatic cancer 126

TEPA

- for chronic leukemia 130
- for Hodgkin's disease 128
- pharmacology 142

Testicles malignancy surgery

for 173

Testosterone

- complications from 136
- for female breast cancer 119
- pharmacology and dosage 135
- for solid tumors 127

Tetracaine *see* Pontocaine**6-Thioguanine** 145**ThioTEPA**

- for chronic leukemias 130
- complications from 143
- pharmacology and dosage 142 ff

Thoracotomy nerve block for pain after 69**Thorax malignancy**

- see also* Respiratory tract
- nerve blocks for 59 ff 66 f
- neurosurgery for 69 109
- spinothalamic chordotomy 94 ff
- surgery for 152 ff

Thorazine *see* Chlorpromazine**Throat malignancy**

- nerve block for 52
- neurosurgery for 110
- root section for 92 f

Thyroid gland

- function in I^{131} therapy 186
- malignancy
 - I^{131} therapy for 186
 - nerve block for 57

surgery for 154

Tic douloureux nerve root section for 91**Tolerance**

- cross tolerance of drugs 17
- in drug addiction method of estimation of 16 f

Tongue malignancy

- nerve block for 54 f 56 f
- surgery for 154

Tracheobronchial tree malignancy

- nerve block for 59 f
- surgery for, 152 ff

Tracheotomy 154 ff**Tractotomy spinothalamic** 97 ff

- complications from 97 ff

Triethylene amine *see* TEM**Triethylene phosphoramidate** *see* TEPA**Triethylene thiophosphoramidate** *see* ThioTEPA**Tumors**

- large ulcerated bleeding—surgery for lesions of 175 ff
- local extensions of—radiation therapy for 188 ff

U**Upper extremities**

- edema after treatment for breast carcinoma 189
- malignancy
 - nerve blocks for 58
 - complications from 58 62
 - surgery for, 177
- pain after amputation—nerve section for 87

Uremia 149 170 172
Ureterostomy 168
Ureters malignancy surgery
for, 168 f 170

Urethane
for acute leukemia 131
for chronic leukemia 130
complications from 141
for multiple myeloma 132
pharmacology and dosage
141

Urinary diversion 168 ff 172
with radiation therapy, 169

Urinary incontinence 170 174

Urinary tract
see also Kidney
surgery for lesions of 167 ff

Uterus malignancy nerve
block for 78 82

V

Vasopressin replacement

after hypophysectomy
123

Vasoxyl see Methoxamine

Veins iliac malignancy sur-
gery for 171

Vulva malignancy surgery
for 173 177

W

Withdrawal syndrome see
Addiction

X

X ray therapy see Radiation
therapy

Y

Yttrium radioactive
for hypophysectomy 188
for prostatic cancer 128